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CHEMICAL CARCINOGENESIS: A REVIEW

BY

I. HIEGER

The Chester Beatty Research Institute, Royal Cancer Hospital, London

(RECEIVED FOR PUBLICATION, JUNE 9, 1948)

Twenty authors who are themselves engaged in some branch of the chemical aspect of cancer research have contributed eighteen well documented specialist articles to a double number of the *British Medical Bulletin*.*

Chemistry of Carcinogenic Compounds.

The first of the eighteen articles, which is by Haddow and Kon, on the chemistry of carcinogenic compounds, begins with Percival Pott (1775) and leads the history of the subject via Yamagiwa to Kennaway's work on synthetic tars (Kennaway, 1924, 1925; Kennaway and Hieger, 1930) and his discovery† of the first cancer producing hydrocarbon, 1 : 2 : 5 : 6-dibenzanthracene (Fig. 1).

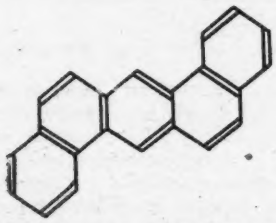


FIG. 1.—1 : 2 : 5 : 6-dibenzanthracene.

The Benzanthracene Story.—The application of fluorescence spectroscopy to the study of carcinogenic substances proved to be the indispensable technique, in Kennaway's words "the single thread that led all through this labyrinth," for the success of his work and, of course, for the tracking down and isolation of 3 : 4-benzpyrene (fig. 2) from pitch.

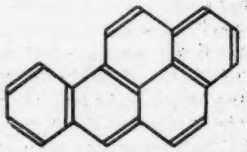


FIG. 2.—3 : 4-benzpyrene.

Fluorescence spectra had suggested that a derivative of 1 : 2-benzanthracene (fig. 3) was the

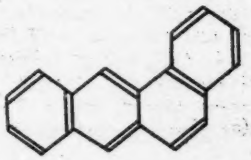


FIG. 3.—1 : 2-benzanthracene.

carcinogenic factor in tar, and in fact such proved to be the case, for whatever terminology is applied to benzpyrene, its structural relation to 1 : 2-benzanthracene is unmistakable and the similarity is supported by the extraordinarily close resemblance of the two fluorescence spectra, which are rather different from the spectrum of 1 : 2 : 5 : 6-dibenzanthracene.

As soon as one carcinogenic hydrocarbon became known, research was set going on the synthesis and testing of other hydrocarbons which were chemical variations on the structure of dibenzanthracene. Benz-rings were added and substracted, alkyl groups were substituted in different positions in the nucleus, hexagon rings were replaced by pentagon rings, C was substituted by N and by S, and as a result of all this activity the number of compounds which have been tested for carcinogenic activity must now be counted in thousands. Hartwell's compilation (published in 1941 from the U.S. National Cancer Institute) catalogues along with authors, references, mode of administration of the compounds, and

* *British Medical Bulletin*, Vol. 4, nos. 5 and 6, 1947, price 10s.
The writers are:
Haddow, A., and Kon, G. A. R.: "The Chemistry of Carcinogenic Compounds."
Berenblum, I., Holiday, E. R., and Jope, E. M.: "Some Physical Methods of Investigating Carcinogenic Hydrocarbons."
Haddow, A.: "Mode of Action of Carcinogens."
Berenblum, I.: "Co-Carcinogenesis."
Crabtree, H. G.: "Anti-Carcinogenesis."
Dickens, F.: "The Influence of the Solvent on the Carcinogenic Response."
Boyland, E., and Weigert, F.: "Metabolism of Carcinogenic Compounds."
Hieger, I.: "Carcinogenic Substances in Human Tissues."
Peacock, P. R.: "The Carcinogenic Action of Heated Fats and Lipoids."
Burrows, H., and Horning, E. S.: "Oestrogens and Neoplasia."
Dodds, E. C.: "A Note on the Carcinogenic Action of Stilbene Derivatives."
Bonser, G. M.: "Experimental Cancer of the Bladder."
Bielschowsky, F.: "The Carcinogenic Action of 2-Acetylaminofluorene and Related Compounds."
Orr, J. W.: "The Production of Liver Tumours by Azo Compounds."
Henry, S. A.: "Occupational Cutaneous Cancer Attributable to Certain Chemicals in Industry."
Currie, A. N.: "The Role of Arsenic in Carcinogenesis."
Goldblatt, M. W.: "Occupational Cancer of the Bladder."
Haddow, A.: "Chemotherapy of Cancer."

† For a slightly more detailed description see Hieger, Symposium on Tar and Pitch Cancer in the *British Journal of Radiology*, vol. 20, 1947, p. 145.

carcinogenic potencies, nearly seven hundred compounds.

If all the publications on the different branches of cancer research were classified it would be found that, with the exception perhaps of the technique and theory of radiation therapy in cancer, the study of chemical carcinogens would head the list in respect of numerical precedence. The reasons for this flood of papers are obvious; the technique of organic synthesis is highly developed, and the tests can be carried out by the simplest means. Nevertheless, no really satisfactory generalization relating structure to carcinogenesis has yet been drawn from the study of these numerous compounds; and, indeed, as the number of carcinogens continues to increase, generalization will become more and more difficult, since it will be necessary to explain the activity of compounds of widely different structure.

On close examination any generalization that has been drawn can be shown to be merely a re-statement in more imposing language of the known facts.

At first it was thought that the mere addition of substitution groups in the benzanthracene molecule would suffice to confer carcinogenicity; then it was found that the group (for example CH_3) must be in certain positions on the molecule. Further, it became clear that the position of the additional benz-ring in 1 : 2 : 5 : 6-dibenzanthracene (fig. 1) was critical because the analogues 1 : 2 : 7 : 8-dibenzanthracene (fig. 4) and 1 : 2 : 3 : 4-dibenzanthracene (fig. 5) were almost inactive.

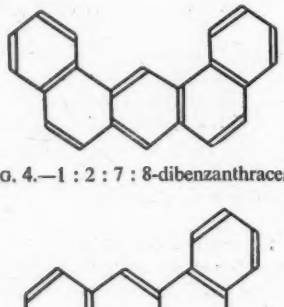


FIG. 4.—1 : 2 : 7 : 8-dibenzanthracene.

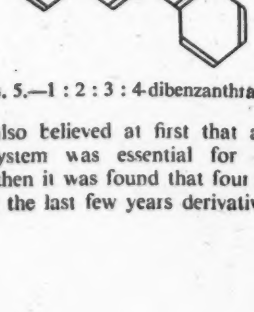


FIG. 5.—1 : 2 : 3 : 4-dibenzanthracene.

It was also believed at first that a condensed five-ring system was essential for carcinogenic potency; then it was found that four rings would suffice; in the last few years derivatives of three-ring systems have been shown to be carcinogenic; and, finally, urethane (ethyl carbamate) must represent the simplest carcinogen to date.

It soon became obvious that simple variations in the chemical structure of a carcinogenic compound could profoundly influence the potency. For example, 1 : 2-benzanthracene is almost inactive carcinogenically, and the insertion of a methyl group in position 1′ or 2′ or 3′ or 3 is without effect, but when the group is in position 4, carcinogenic potency begins to appear, in position 5 the potency is quite high, and in 9 or 10 it is at its maximum; and when both 9- and 10- are substituted the resulting compound, 9 : 10-dimethyl-1 : 2-benzanthracene (fig. 6), represents the most potent carcinogenic compound known.

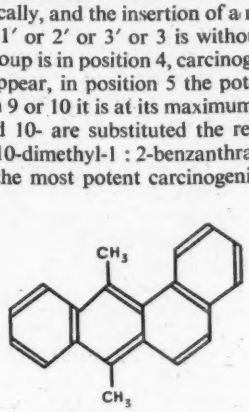


FIG. 6.—9 : 10-dimethyl-1 : 2-dibenzanthracene.

Further work soon revealed unsuspected difficulties in the effort to correlate chemical structure and carcinogenic potency. For example, the introduction of a third and fourth methyl group decreased the activity of the compound; and if the two methyl groups were disposed in certain positions, 1′ : 10 or 3 : 9-, the resulting dimethyl-dibenzanthracenes showed no activity when they were tested biologically.

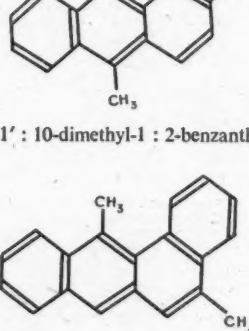


FIG. 7.—1′ : 10-dimethyl-1 : 2-benzanthracene.

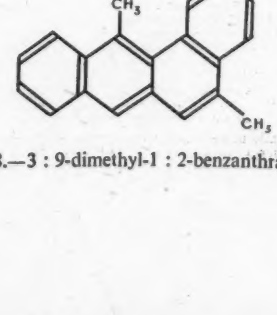


FIG. 8.—3 : 9-dimethyl-1 : 2-benzanthracene.

Technique of Testing Carcinogens

Haddow and Kon assume that the reader is familiar with the technique of testing the carcinogens, but a brief description here may interest the reader. The two commonest methods of testing are either to paint a solution of the compound, in benzene or acetone or liquid paraffin, on the interscapular skin of the mouse twice a week until papillomas and then epitheliomas appear; or alternatively, to inject a solution of the compound, in lard or vegetable oil or tricaprylin or cholesterol, subcutaneously into the mouse: often one injection only is given.

The potency is measured by the proportion of tumours obtained, by the length of the latent period, or by some combination of both, but such estimations are rather approximate especially if the activity is not very pronounced. In Tables 1, 2, and 3, taken from the paper by Hieger (1947) referred to above, are reproduced results of experiments on quantitative tumour production.

Table 1

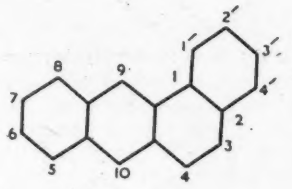
TUMOUR PRODUCTION IN MICE BY CARCINOGENIC HYDROCARBONS: TABLE SHOWING DIFFERENCES IN CARCINOGENIC POTENCIES MEASURED BY VARIATIONS OF (a) LATENT PERIOD, AND (b) YIELD OF TUMOURS

	Average latent period (days)		Tumours*
	Subcutaneous application	Skin application	
Methylcholanthrene ..	91	126	
1 : 2 : 5 : 6-dibenzanthracene	165	213	
3 : 4-benzpyrene	107	144	
9 : 10-dimethyl-1 : 2-benzanthracene		43	13/20
Methylcholanthrene (*a*) ..		99	18/18
Methylcholanthrene (*b*) ..		151	5/8
3 : 4-benzpyrene (from pitch)		127	10/10
3 : 4-benzpyrene (synthetic)		109	7/9
Cholanthrene		112	28/49
10-methyl-1 : 2-benzanthracene		147	12/18
3 : 4 : 8 : 9-dibenzpyrene ..		205	10/17
1 : 2 : 5 : 6-dibenzanthracene		239	41/65
1 : 2 : 5 : 6-dibenzacridine		350	6/25

* Numerator = tumour mice; denominator = total mice.

Other Aromatic Condensed Ring Compounds.—To some degree the benzanthracene story was repeated with other aromatic condensed ring compounds. Thus chrysene, phenanthrene, fluorene, and even anthracene turned out to be the inactive parent hydrocarbon of carcinogenic derivatives, which were synthesised by introducing methyl groups or additional benz- or penta-rings into the molecule. Thus 1 : 2-dimethylchrysene (fig. 9), 3 : 4-benzphenanthrene (fig. 10), 1 : 2 : 5 : 6-dibenzfluorene (fig. 11), 9 : 10-dimethylanthracene (fig. 12), and 5 : 10-dimethylene 1 : 2-cyclopentenoanthracene (fig. 13) all showed carcinogenic potency.

Table 2



TUMOUR PRODUCTION IN MICE (METHYL DERIVATIVES OF 1 : 2-BENZANTHRACENE): TABLE SHOWING EFFECT OF MINOR ALTERATIONS IN MOLECULAR STRUCTURE ON CARCINOGENIC POTENCY

	Skin application*	Subcutaneous application*
1'-methyl	0	..
2'-methyl	0	..
3'-methyl	0	..
3-methyl	0	..
4-methyl	1/10	..
5-methyl	5/10	17/20
6-methyl	3/10	..
7-methyl	0	1/19
8-methyl	?	..
9-methyl	3/20	17/20
10-methyl	11/20	26/30

* Numerator = tumour mice; denominator = total mice.

Table 3

TABLE SHOWING EFFECT ON CARCINOGENIC POTENCY OF PROGRESSIVE DILUTION OF THE DOSE OF CARCINOGEN (SUBCUTANEOUS INJECTION)

mg. 1:2:5:6-dibenzanthracene	No. of mice	Tumour mice	Tumours per cent.	Mean latent period—months
0·01	328	37	11	..
0·005	364	13	4	..
0·0025	167	2	1·2	..
0·00125	158	—	—	..
5·0	10	5	50	4·3
2·5	10	8	80	3·8
1·0	10	9	90	3·6
0·5	10	10	100	3·6
0·25	30	26	90	4·6
0·125	20	9	45	6
0·05	10	4	40	7·3
0·0125	20	4	20	8
0·005	20	—	—	—

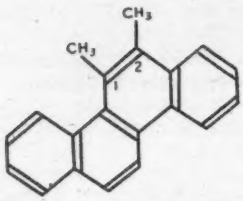


FIG. 9.—1 : 2-dimethylchrysene.

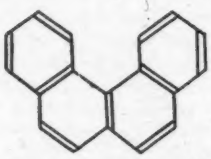


FIG. 10.—3 : 4-benzphenanthrene.

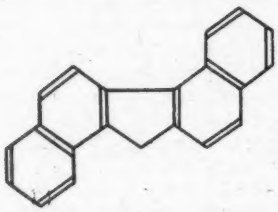


FIG. 11.—1 : 2 : 5 : 6-dibenzfluorene.

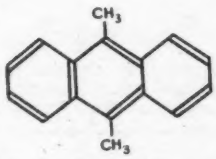


FIG. 12.—9 : 10-dimethylanthracene.

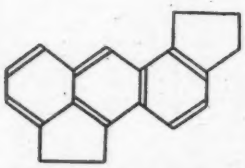


FIG. 13.—5 : 10-dimethylene 1 : 2-cyclopentenoanthracene.

One particular hydrocarbon, 20-methylcholanthrene (figs. 14 and 16) is especially interesting. Cook

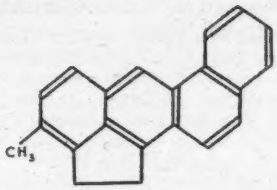


FIG. 14.—20-methylcholanthrene (*a*).

(1933) had found that positions 5- and 6- in the 1 : 2-benzanthracene molecule were of importance in that substitution there conferred carcinogenicity, and that, secondly, the addition of a penta-ring in that position would give a hydrocarbon which was not only a benzanthracene derivative but which could also be considered as a ring-closed and dehydrogenated derivative of deoxycholic acid (fig. 15).

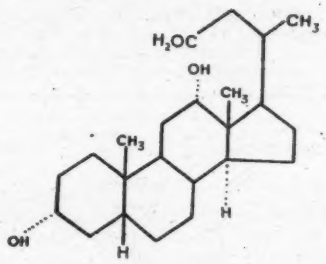


FIG. 15.—Deoxycholic acid.

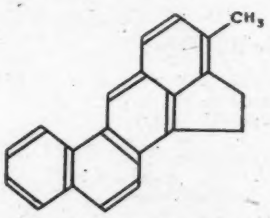


FIG. 16.—20-methylcholanthrene (*b*).

Methylcholanthrene was made from cholic acid and also synthetically, and its powerful cancer-producing activity was useful evidence for the protagonists of the hypothesis that spontaneous human cancer is caused by the operation of endogenic carcinogens derived from sterols, a hypothesis which still awaits proof.

Nitrogen and Sulphur Analogues of Polycyclic Hydrocarbons.—Besides the polycyclic hydrocarbon carcinogens, there are their nitrogen and sulphur analogues such as dibenzacridine (fig. 17), dibenz-

carbazole (fig. 18), and a thiophene-substituted 1 : 2-benzanthracene derivative (fig. 19), all of which are carcinogenic.

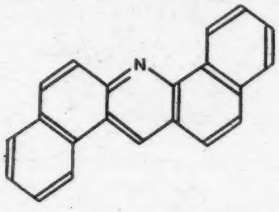


FIG. 17.—1 : 2 : 5 : 6-dibenzacridine.

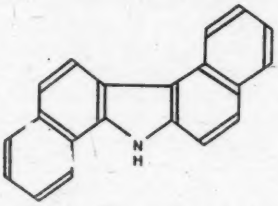


FIG. 18.—1 : 2 : 5 : 6-dibenzcarbazole.

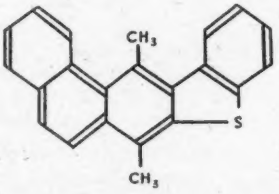


FIG. 19.—4 : 9-dimethyl-2 : 3 : 5 : 6- dibenz-thiophanthrene.

Simpler carcinogens are known, examples of which are 2-anthramine (fig. 20) and 2-acetylamino-fluorene (fig. 21), and a further step away from the

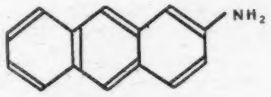


FIG. 20.—2-anthramine.

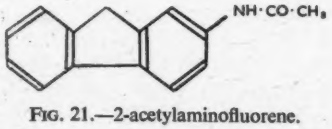


FIG. 21.—2-acetylaminofluorene.

original type of carcinogenic hydrocarbon is shown by the structure of the active liver-cancer-producing azo dyes, the best known example being butter yellow, 4-dimethylaminoazobenzene (fig. 22). The

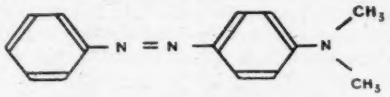


FIG. 22.—4-dimethylaminoazobenzene (" butter yellow").

aminostilbenes, for example 4-dimethylaminostil-bene (fig. 23), which can be regarded as analogues

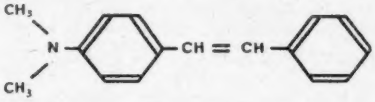


FIG. 23.—4-dimethylaminostilbene.

of the azo dyes, were found to be carcinogenic by Haddow in the course of his work on growth inhibition by carcinogenic hydrocarbons. This compound, and also 2-anthramine and 2-acetyl-aminofluorene, have the peculiarity of producing tumours in the rat in a considerable variety of tissues in the body as well as at the site of injection.

Physical Methods of Investigating Carcinogenic Hydrocarbons

The discovery of the carcinogenic hydrocarbons and the isolation of 3 : 4-benzpyrene from pitch was largely due to the fortunate circumstance that the intense fluorescence of the hydrocarbon is highly characteristic and that it is able to overcome the combined fluorescences of the hundreds of other compounds present in that complex mixture. Naturally, fluorescence spectroscopy, first applied by Mayneord and exploited by Hieger, has been the principal physical method used in the study of carcinogenic hydrocarbons.

Berenblum has demonstrated that by using a moving wedge technique a more quantitative measure of the characteristics of the fluorescence spectrum can be obtained to assist in the identification of fluorescent derivatives of hydrocarbons, and a similar refinement has been developed by Holiday for absorption spectroscopy. These two methods have been employed to check identity and to estimate hydrocarbons quantitatively, for example, the disappearance rate when they are applied to the skin or injected into animals.

An interesting calculation shows that 10^{-7} μg. benzpyrene per cell could be detected if use were made of the Caspersson method of micro-spectrography in monochromatic ultra-violet light. This quantity represents a rather high concentration of hydrocarbon, namely 2 μg. per mg. or 2 mg. per g. of tissue. The minimum quantity required for carcinogenesis is still uncertain for a number of rather obvious reasons. For example,

after a hydrocarbon is injected, it can be quantitatively recovered after the tumour appears (Shear), suggesting that carcinogen is not used up in the carcinogenic process and that the rate of elimination has nothing to do with carcinogenesis but with the mechanisms which are anti-carcinogenic, that is, the de-toxication and excretory apparatus.

> "The dosage of hydrocarbon required to initiate a tumour is often, however, far lower than that used in these metabolic experiments, and it remains uncertain whether the fraction of the hydrocarbon which is instrumental in carcinogenesis follows the same metabolic path as the bulk of material. The minimal doses for carcinogenesis are probably too low for standard spectroscopic techniques to be applicable."

The absorption-technique will probably prove more useful than fluorescence in tracing the fate of minute amounts of carcinogens in the tissues, since a slight chemical change can extinguish the fluorescence while only moderately altering the absorption spectrum.

Mode of Action of Chemical Carcinogens

The first step in the attack on this baffling problem was, of course, to try to find some parallel between chemical structure and carcinogenic activity. Much has been written on this subject, but always *en arrière*; that is, explanations have been put forward after the two properties had been found together, and the position has become more difficult as each new carcinogen is discovered. Haddow is careful to point out that none of these hypotheses are as yet satisfactory, either because sooner or later exceptions are found to any generalization, or because it has not yet been possible to carry out an adequate test of their validity. To find a theory relating carcinogenic mechanism and chemical constitution which will embrace the structures of hundreds of carcinogens ranging from 4'-dimethyl-aminostilbene to 3 : 4-benzpyrene, from acetylamino-fluorene to 1 : 2 : 5 : 6-dibenzanthracene, or from 430-styrol to urethane, presents a formidable task. For example, of the three benzanthracene derivatives, 9 : 10-dimethyl-1 : 2-benzanthracene (fig. 24), 9 : 10-dimethyl-1 : 2 : 7 : 8-dibenzanthracene (fig. 25), and 9 : 10-dimethyl-1 : 2 : 3 : 4-dibenzanthracene (fig. 26), the first two are carcinogenic, and the third is inactive. This difference is explained by the absence of an essential phenanthrene double bond, shown by asterisks in the formulæ. Furthermore, of the three dibenzphenanthrenes, 1 : 2 : 3 : 4-

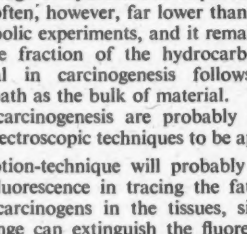


FIG. 24.—9 : 10-dimethyl-1 : 2-benzanthracene.

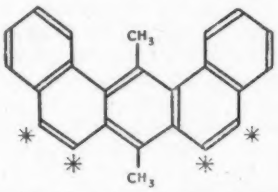


FIG. 25.—9 : 10-dimethyl-1 : 2 : 7 : 8-dibenzanthracene.

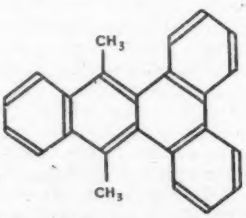


FIG. 26.—9 : 10-dimethyl-1 : 2 : 3 : 4-dibenzanthracene.

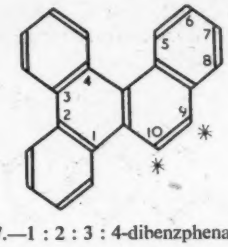


FIG. 27.—1 : 2 : 3 : 4-dibenzphenanthrene.

FIG. 28.—9-methyl-1 : 2 : 3 : 4-dibenzphenanthrene.

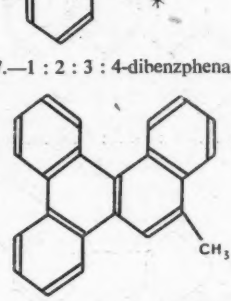


FIG. 29.—10-methyl-1 : 2 : 3 : 4-dibenzphenanthrene.

dibenzphenanthrene (fig. 27), 9-methyl-1 : 2 : 3 : 4-dibenzphenanthrene (fig. 28) and 10-methyl-1 : 2 : 3 : 4-dibenzphenanthrene (fig. 29), only the first is active ; again this difference is accounted for by the unsubstituted phenanthrene bond being absent in the 9-methyl and 10-methyl derivatives.

However, no explanation is offered of why 1 : 2-benzanthracene (fig. 3) is inactive but that substitution in the 3 or 4 position by methyl not only fails to interfere with the important phenanthrene double bond but actually confers carcinogenic activity on the parent hydrocarbon.

Physical Theory Applied to Carcinogenic Hydrocarbons.—Physical theory has been applied to the study of carcinogenic hydrocarbons by Schmidt (1924) and by Pullman (1945, 1946) and Daudel (1946), and it has been proposed that the electron density at the phenanthrene double-bond position in the benzanthracene molecule must be above a critical limit for carcinogenic potentiality to appear. The order of electron density in different compounds approximately corresponds with what would be expected from the order of biological potencies of a series of carcinogens.

The Pullman technique requires the solution of 2,000 simultaneous equations for obtaining a numerical value for characterizing the electron density, in a single compound ; consequently very few investigators are likely to undertake such a laborious task.

The terminology is highly technical :

> "In the aminostilbenes it would seem to be a necessary condition, although clearly not a sufficient one, that the molecule should be capable of assuming a quinonoid disposition, with an electron-donating group in one ring conferring a high degree of negative polarity in the other and the outstanding feature being the necessity for unsubstituted hydrogen atoms in the ethylene bridge and at the p′ position. Such a system would appear not merely to contain a structure in the ethylene bridge which is analogous with the phenanthrene double bond in the cyclic hydrocarbons, but to possess electronic characters which are produced in condensed systems of benzene rings by rather different means."
>
> "... a necessary condition of carcinogenic activity is that the density of such regions should exceed 0·44e/Å^2 ; in particular, he further suggested that the activity of a carcinogen is due to the electro-affinity of its excited state facilitating a quantal change in neighbouring molecules. More recently A. and B. Pullman (1946) and Martin (1946) have obtained supporting evidence of this conception through a quantum mechanical treatment (with Daudel) which permits a calculation of the density of electrons for a given structure (in chrysenes, benzanthracenes, and benzacridines) by means of which it is claimed that a relation can be formulated between carcinogenicity and the electronic density of the region K, the density-threshold below which a substance ceases to be carcinogenic being 1·292e."

However, as has been aptly pointed out, the test for any such theory relating structure and carcinogenic activity would be its capacity to assess the activity of a compound *before* and not *after* the biological test.

Order of Carcinogenic Potency.—Fieser has pointed out that the order of carcinogenic potency of the hydrocarbons is the same as the order for substitution reactivity in diazo coupling, oxidation with lead tetra-acetate, or perbenzoic acid, and condensation with sulphur monochloride. The awkward fact that some anthracene derivatives also show high reactivity is circumvented by the explanation that the carcinogen must also possess additional properties such as suitable solubility, adsorbability, and molecular size. He suggests that in the carcinogenic process the S- groups in tissue proteins

$$\begin{array}{c} \\ | \\ \text{S-} \end{array}$$

are converted to the structure

$$\left.\begin{array}{r} \text{Hydrocarbon-S-} \\ \text{SH-} \end{array}\right\} \text{proteide,}$$

but only evidence by analogy is offered in support of this possibility.

Fieser found that the catalytic hydrogenation of methylcholanthrene resembles enzymic reactions and results in the addition of H_2 at positions other than the centres usually accepted as the most reactive, that is the meso positions, and that this reaction is much slower than meso substitution. In the example given, methyl-cholanthrene adds an H_2 at the reactive phenanthrene double-bond position if this hydrocarbon is considered structurally as a 1 : 2-benzanthracene derivative, which would be in agreement with the phenanthrene bond theory.

The metabolic products of hydrocarbons which can be isolated in feeding experiments on rats and rabbits (Boyland and Levi, 1935, 1936) shows that *in vivo* the points of attack are neither the reactive meso position nor the phenanthrene double bond (the K-region) but the 4′ 8′ positions for 1 : 2 : 5 : 6-dibenzanthracene and the 4′ position for 1 : 2-benzanthracene, although there is little evidence that these metabolites represent more than a mere fraction of the total metabolic products.

Fieser is quoted as saying,

> "... the assumption that the metabolic change follows a fundamentally different reaction mechanism from the postulated substitution reaction of carcinogenesis seems necessary in order to account for the

fact that the attack occurs at a part of the molecule different from that involved in substitutions."

The writer confesses to being somewhat puzzled by this quotation. It is surely unjustified to derive an " assumption " from a " postulation " based on a " fact " which is required to be proved.

Fieser suggests that, since substitution reactions bear an order-parallelism with carcinogenic potency, substitution is closely associated with the carcinogenic mechanism; but as meso-substituted 1 : 2-benzanthracene derivatives are the most powerful carcinogens, the carcinogenic substitution probably takes place elsewhere in the molecule, namely at the position of secondary reactivity, the phenanthrene double bond. Why, then, does substitution induce carcinogenic potency into the molecule? It can hardly be because the remaining H atom is specially activated for the substitution reaction, for if either of the H atoms in the phenanthrene double bond of 1 : 2 : 3 : 4-dibenzphenanthrene is substituted by CH_3 the carcinogenic potency disappears.

Sulphur-linkage.—Crabtree also considers that the sulphur linkage is the point of attachment of the carcinogen to the tissue components, because compounds which competitively attach themselves to S-groupings inhibit carcinogenesis by hydrocarbons. These inhibitors include brombenzene and the simpler polycyclic aromatic hydrocarbons, anthracene, phenanthrene, and naphthalene. If this explanation were true one would then have to explain why tar, which is the source of all these simple hydrocarbons, is carcinogenic. Assuming that the carcinogen *is* attached to a tissue component by a S-linkage, one is tempted to ask, what happens next?

Biological Aspects of Carcinogenesis.—With regard to the biological aspect of carcinogenesis, Haddow proposed that the process is set in motion by the inhibition of the growth of normal cells finally leading to the domination of the tissue by those cells which have successfully adapted themselves to the new conditions. Some of the cells are immune to the inhibitory action of the carcinogen.

It would be interesting to know, and such experiments have probably been tried, if local injection can be influenced by simultaneous remote treatment.

The adapted strain of cells is supposed to be a mutant form of normal cells, an explanation of cancerous change which is nearly as old as the mutation theory itself; but, until cancer cells can be crossbred, evidence for mutation theory in cancer cannot be completely satisfactory.

Haddow draws on analogies with experiments on strains of Neurospora, where mutations are induced by variations in the available amino acid supply, but it might perhaps be objected that one of the most powerful mutagens (mustard gas) is an anti-carcinogen. In favour of the mutation theory for carcinogenesis is the discovery of Strong that the descendants of mice treated with methyl-cholanthrene become mutated for coat colour and for incidence of spontaneous gastric cancer, and secondly, Demerec has found that the carcinogens are also potent mutagens for Drosophila. Carcinogens, ultra-violet light, *x* rays, and raised temperature all facilitate mutations in Drosophila, and all these agents have carcinogenic capacity for mammalian and avian tissues.

Haddow then embarks on a somewhat daring theory of carcinogenesis. Schrödinger, in his book *What is life?* describes a gene mutation as the product of a quantum jump in the gene molecule resulting in a new gene possessing an altered configuration. The problem of mutation thus is reduced to the question, how is the energy to be supplied to the electrons of the gene molecule to make them jump?

The answer is, by radiation (that is, carcinogenic radiation) or by the energy liberated during the chemical transformations which are undergone by the carcinogen in changing to its metabolic derivatives. Again, until evidence is forthcoming, such speculation—however attractive—must remain purely imagination, for notwithstanding the great beauty of Schrödinger's exposition, its applicaton to chemical carcinogenesis depends in the first place on the adequacy of a further theory, that carcinogenic transformation is indeed a mutation.

By analogy with the discoveries of Sonnebornon cytoplasmic inheritance in Paramicium, Haddow propounds the hypothesis that virus tumours contain the controlling mutagen, that is the virus, in the cytoplasm as a cytogene or plasmagne (anything but a *nuclear*-gene). From this description of the conditions in virus tumours it is bu a step to the idea that in mammalian tumours not transmissible by filterable viruses similar mutagns in the form of autosynthetic proteins or enzynes form a more labile and integrated part of he tumour cell such that attempts at separation in these cases by the crude methods now available destroy the mutagenic structures. To complete he edifice of theories one further idea is necessay, that the chemical carcinogen causes some self-duplicatory protein in the normal cell to mutateto a " 'rogue' enzyme upon which the newly acquied growth-properties may possibly depend," and it is only required to substitute " mutated gene " or " rogue enzyme."

Co-Carcinogenesis

Co-carcinogenesis is defined by Berenblum as "augmentation of tumour production resulting from a direct local effect on a tissue," to distinguish it from (*a*) promoting effects induced by alteration in the diet in experimental liver tumours induced by dimethylaminoazobenzene, called "pro-carcinogenic" effects, and from (*b*) the effects of the solvent on a carcinogenic hydrocarbon *in situ*, where alteration in the vehicle probably alters the elimination rate of the agent.

The earliest experimental co-carcinogenic agencies were wound healing, freezing with carbon-dioxide snow, mechanical irritation, subcutaneous fibrosis, radiation of all kinds, the basic fraction of creosote oil and—most effective of all—croton oil. Chemical irritants are by no means always co-carcinogens and even the members of the above list must be applied in suitable doses for their effects to be detected. Berenblum has concluded from the data of experiments with co-carcinogens that the carcinogenic process proceeds by stages: (1) pre-carcinogenesis, where some fundamental change is brought about in normal cells preparing them for the second stage; (2) epicarcinogenesis, the actual conversion to neoplasia; and (3) metacarcinogenesis, the transformation of benign growths to malignant tumours.

Carcinogens proper can carry out all three stages but co-carcinogens can only carry out stages 2 and 3. Thus he has found that a single application of a carcinogen will irreversibly convert some cells in mouse skin to the preneoplastic condition; all the subsequent changes can at any later time be effected by croton oil. The phenomenon has been clearly observed by Rous and Kidd (1941) in the tarring of rabbits, where the warts are very liable to regress and require co-carcinogens (wound healing, further tarring, application of chloroform or turpentine) for the growth of the warts to be maintained. Rous proposes that the first change in the normal cells be termed "initiation" (Berenblum's pre-carcinogenesis") and that the second stage be called the "promoting" process (Berenblum's "epi-carcinogenesis").

It has been found that if a carcinogenic hydrocarbon is applied once to the skin of a mouse, which is then left untreated for twenty weeks, the application of croton oil will then bring about tumour formation. Since hydrocarbon can no longer be detected after a very few weeks, and since the turnover rate of the cells in the skin must also contribute to the removal of the original effects of carcinogen, it follows that the pre-carcinogenic cells must be self-duplicating so as to leave behind some cells that are ready for epi-carcinogenesis. In other words, one painting with carcinogen rapidly 'mutates' some skin cells to the pre-carcinogenic state, or, one treatment with carcinogen permanently alters the skin.

Although Berenblum can show the co-carcinogenic effect by demonstrating a great increase in the total number of tumours evoked by diluted carcinogenic hydrocarbons and by revealing irreversible changes in cells which have been converted into potential tumour cells, no experiments have yet succeeded in showing co-carcinogenic action to be capable of raising the carcinogenic potency of feeble or slow-acting carcinogens.

Anti-Carcinogenesis

Crabtree in his article on anti-carcinogenesis gives a list of the agents for which inhibitory action has been claimed: "Mustard gas and a few of its oxidized and substituted derivatives, cantharidin, carbon-dioxide snow, heptaldehyde, a phenolic fraction of tar, simple substances containing a labile halogen atom, p-thiocresol, strong sunlight and organic peroxides, acid chlorides, the mercapturate forming hydrocarbons, naphthalene, anthracene, and phenanthrene."

It should be noted that two of the agents in this list are known to be also cancer producers and further, when the inhibition tests were repeated by other workers, in some cases it was impossible to obtain confirmation of earlier results, which was probably due to differences in the conditions under which the agents were tested and also to variations in the biological material.

Experiments on a series of chlorine-containing compounds has shown that a relation exists between their efficiency as inhibitors both of tumour induction and of tissue glycolysis; they probably operate via hydrochloric acid liberation by hydrolysis, for the order of lability of the chlorine was the same as the order of inhibitory power.

The halogen compounds can also act directly by condensing with SH-containing cell components, thus impairing the efficiency of those enzyme systems dependent on intact SH-groups for their proper functioning; examples of this type of inhibitor are brombenzene, maleic and citraconic acids, heptaldehyde, and mercapturate-forming hydrocarbons. All these compounds deplete the skin of glutathione and are antagonistic to cancer production in the skin, and Crabtree therefore puts forward the speculation that some reaction between carcinogen and SH- grouping of constituents of tissues is essential for tumour induction.

He is, however, careful to point out the tentative nature of these speculations by the plentiful use of that overworked word "may."

"The work of Weigert and Mottram (1946) on the metabolism of 3 : 4-benzpyrene, by the aid of fluorescence spectra, has shown that a series of intermediate compounds can be identified between the hydrocarbon itself and the final oxidized derivatives which are excreted. These intermediates contain radicals derived from unknown cell-constituents, and may conceivably represent the true carcinogens. The coupling may well involve SH-groups, and recalls the surmise of Wood and Fieser (1940), based on considerations of the special chemistry of 3 : 4-benzpyrene, that such a fixation may be an initial stage in the carcinogenic process."

The induction of liver tumours in the rat and mouse by feeding 4′-amino-2 : 3′-azotoluene or N : N-dimethyl-p-aminoazo-benzene, can be inhibited by alterations in the diet. This inhibition or rather protective effect is shown by substituting wheat, rye, or millet by rice bran, yeast, liver, casein, and riboflavin, casein and B vitamins, or by dried whole milk and carrot, but biotin stimulates liver-tumour production by azo dyes.

The metabolic oxidative products of the azo dyes are inhibitory for a number of enzyme systems, and it has been suggested that the dye acts carcinogenically via an oxidized product which attacks the SH-group of the enzyme. It is a little difficult to reconcile this hypothesis with the non-carcinogenicity of the oxidized end products, but perhaps no more difficult than to explain why tar should be carcinogenic, since it is full of mercapturate-forming hydrocarbons like anthracene, phenanthrene, and naphthalene which Crabtree and also Lacassagne have reported to inhibit tumour production by the carcinogenic hydrocarbons. Crabtree refers to the notable work of Tannenbaum who found that animals on a diet deficient in calories show inhibition of spontaneous and artificially induced cancer. Animals on such diets are stunted and have atrophic endocrine systems, which would account for the failure to develop breast cancer.

The Influence of the Solvent on the Carcinogenic Response

Dickens describes the effect of solvent on the rate of appearance and total number of tumours produced when benzpyrene in solution in a variety of solvents is injected subcutaneously into mice.

The effect of varying the solvent has been investigated by a number of workers, the majority agreeing that carcinogens dissolved in the fat of the same species as the animal undergoing injection show decreased potency, while oils such as arachis and olive oil increase the potency, as also does the addition of cholesterol. If the solution of carcinogen is painted on the skin instead of being injected, results sometimes occur showing the opposite effects.

Dickens uses as standard technique 0·3 mg. benzpyrene dissolved in 0·3 c.cm. tricaprylin injected subcutaneously into pure-strain mice; he rightly points out that the use of more carcinogen than is necessary for an optimal yield of tumour will only mask any inhibitory effect.

The decrease of carcinogenic efficiency when the hydrocarbon is dissolved in mouse fat has been confirmed, and purification of the fat indicated that the fraction possessing inhibitory powers is concentrated in the phospholipid part which can be removed by extraction with acetone.

Addition of 3 per cent. cholesterol to the tricaprylin solution of benzpyrene raised the total of tumours from about 45 per cent. to over 80 per cent.; 0·3 c.cm. ox-brain lipids containing 0·3 mg. benzpyrene gave only one tumour in twenty-nine mice. Ox-brain lipids were the most potent inhibitors, followed by fresh mouse fat, then by mouse fat freed from phospholipids by acetone, which when used as solvent for benzpyrene gave a yield of tumours differing only slightly from the controls injected with benzpyrene in tricaprylin. Two phospholipids (cephalin and lecithin) had only a moderately retarding effect on the development of tumours, which suggests that either fresh mouse fat must contain some other inhibitor, or the phospholipids are present in some peculiar state.

Estimation of hydrocarbon in whole animals at different times after injection showed that mice which had received solutions containing cholesterol (that is, the most efficient tumour producers) had eliminated the hydrocarbon much the most rapidly (from 0·3 mg. only 0·001 mg. was left in 82 days), while the animals injected with the less effectively carcinogenic solutions containing hydrocarbon plus lecithin and cephalin retained hydrocarbon for a much longer period (from 0·3 mg., 0·065 mg. was left in 82 days).

Such a result is unexpected particularly if it be noted that the first of the twenty-three tumours in the cholesterol series did not appear until the seventieth day, when more than 99 per cent. of the hydrocarbon had already been eliminated. Dickens suggests that these data support the metabolite theory of carcinogenesis, which postulates that the hydrocarbon has first to be converted to a derivative, the true carcinogen; he proposes that the phospholipids behave as anti-oxidants by retarding the conversion to the effective carcinogenic agent. The anti-oxidation effect on hydrocarbons of phospholipids could be confirmed *in vitro*; but cholesterol, which would be expected to show pro-oxidation properties in line with its capacity for tumour

facilitation, showed no acceleration of oxidation *in vitro*.

Hydrocarbons when dissolved in purines disappear very rapidly on injection, but low incidences of tumours result; hence, Dickens concludes that a distinction must be made between physical and chemical elimination of carcinogen and that the tumour inhibitory solvents act by retarding the oxidation of the hydrocarbon.

Metabolism of Carcinogenic Compounds

Boyland and Weigert's article on the metabolic products of the carcinogenic hydrocarbons is aimed at the elucidation of the mechanism of carcinogenesis by the theory that the true carcinogen is not the hydrocarbon itself but is a metabolite or is the energy liberated in the process of metabolism.

The evidence brought together here in favour of the theory rests on a number of facts, inferences, and analogies. Since the hydrocarbons are insoluble in water, the formation of water-soluble derivatives is required for a water-phase reaction (the possibility of an oil-phase reaction is also mentioned). It might be asked whether the oil-soluble hormones and vitamins have also to be converted to water soluble derivatives for activation.

One of the main supports for the metabolite theory is the fact that 1 : 2 : 5 : 6-dibenzanthracene is almost devoid of carcinogenic effect in one species, the rabbit, but is very potent in the tissues of the rat, and *pari passu* the metabolism of the hydrocarbon is different in the two species. Moreover, differences are also found in the metabolic products of anthracene when it is fed to the rabbit or to the rat.

The hypothesis is advanced that the rat converts 1 : 2 : 5 : 6-dibenzanthracene to a carcinogenic product but the rabbit transforms it to a non-carcinogenic metabolite, or alternatively that the route taken by the hydrocarbon in metabolism is different in the two species, emphasis being laid on the process rather than on the end product.

The theory is not entirely satisfactory for a number of reasons. For example, of the total amount of hydrocarbon administered to the animal, but a mere fraction can be isolated as metabolites of recognizable identity. The fate of the major part of the carcinogen and the chemical constitution of the metabolic products is still undefined. 3 : 4-Benzpyrene when fed to rats or rabbits is excreted as the same two hydroxy derivatives, 8- and 10-benzpyrols, but in different proportions, yet benzpyrene is highly carcinogenic for the rat but only very feebly so in the rabbit.

The majority of the metabolites are non-carcinogenic, and in the very few cases where a hydroxy derivative of a carcinogenic hydrocarbon is found to be carcinogenic its activity is lower than that of the parent hydrocarbon. When anthracene is fed or injected into rats or rabbits, water-soluble derivatives, chiefly the 1 : 2-dihydroxy-1 : 2-dihydroanthracene, are excreted in the urine. A comparison of the melting points and optical rotation of the diol, its acetyl derivative and the glycuronide, shows that the metabolite from the rat and from the rabbit are different, but this difference can be accounted for by the explanation that the rat excretes the optically active diol and its derivatives, while the rabbit excretes the racemic forms. Whether the racemization takes place *in vivo* or *in vitro* has not yet been settled.

1 : 2-Benzanthracene (almost inactive), and 9 : 10-benzanthracene (the most active carcinogen known) both yield the 4′- hydroxy metabolite in rats and mice, suggesting that, in these cases at least, metabolism to a hydroxy derivative is merely a detoxication process, since both carcinogenic and non-carcinogenic hydrocarbons follow the same metabolic path.

From the urine of rats and mice that had been injected with 1 : 2 : 5 : 6-dibenzanthracene, 4′ : 8′-dihydroxy-1 : 2 : 5 : 6-dibenzanthracene was isolated; the constitution of the analogous hydroxy derivative from rabbit's urine is still undecided.

A condensed account then follows of the intermediate stages between benzpyrene and the final metabolite, 8-benzpyrenol. Four substances ($X_1X_2F_1F_2$) have been detected by their fluorescence and absorption spectra, in the tissues and excreta after the hydrocarbon has been painted on the skin or injected, or mixed with the diet.

The successive changes are represented in fig. 30.

The authors' statement "In any case these experiments suggest that it is not the hydrocarbon itself which is the proximate carcinogenic agent but one of the metabolites X_1 or F_1 or the energy released during the transformation from X_1 to F_1," rests on the following data :

F_2 is 8-benzpyrenol, leaving X_1X_2 and F_1 to be dealt with. When the hydrocarbon is painted on mouse skin or injected, X_2 appears slowly and its development is increased by the application of fats which are inhibitory to tumour production (Dickens), and is reduced by croton oil, that is, a tumour-facilitating agent, hence X_2 is not regarded as being involved in neoplastic transformation, leaving X_1 and F_1 to be considered.

No mention is made however, of any attempt to test the carcinogenicity of X_1 or F_1 although these two substances have been separated by Weigert and Mottram by chromatography; and, if their activity is at all comparable with that of benzpyrene,

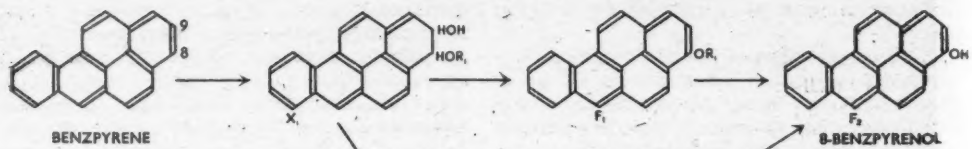


FIG. 30.—Successive changes from 3 : 4-benzpyrene to 8-benzpyrenol.

quite enough material should be obtainable from the skins of a number of mice which could be treated with the hydrocarbon and then extracted.

With regard to the carcinogenic process being dependent on the energy released during metabolism, that would be more difficult to test, but since anthracene and naphthalene undergo metabolic changes analogous to those of carcinogenic hydrocarbons, some carcinogenic energy should be released in all such transformations; nevertheless anthracene and naphthalene remain non-carcinogenic.

The metabolic products of butter yellow (p-dimethylaminoazobenzene) inhibit the enzyme triose-phosphate-dehydrogenase, an essential enzyme in carbohydrate metabolism. Among these metabolites are p-phenylene diamine and N : N-dimethyl-p-phenylenediamine which are non-carcinogenic.

β-Naphthylamine induces bladder tumours in dogs and men but not readily in other species, and, in agreement with the authors' thesis, the metabolic end products are different in the dog and in rats, rabbits, and monkeys; the dog excretes the sulphate of 2-amino-1-naphthol, and the other species secrete 2 acetylamino-6-hydroxynaphthalene.

Carcinogenic Substances in Human Tissues

A number of workers have now confirmed Schabad's discovery in 1937 that a carcinogenic substance can be extracted from the tissues of cancerous human subjects. At first it was thought that only the liver contained the factor, but as more tissues were investigated it was found that livers from patients who had died of other diseases also contained the endogenic carcinogen, and further, that it could be extracted from other organs besides the liver namely, lung, kidney, and muscle.

A difficult problem to be solved in the investigation of these substances is their apparent random occurrence; for example, some livers yield potent carcinogenic extracts while others give inactive preparations. The randomness can also be explained by variations of susceptibility of the experimental mice which are injected with the extracts.

Schabad's first successes were with a crude benzene extract of liver of patients who had died of cancer; livers of non-cancerous subjects gave inactive extracts and saponification of cancer liver did not increase the potency of the preparation; in fact the unsaponifiable fraction of nine cancer livers was inactive.

Steiner (1942, 1943), who has done valuable work in this field, found on the other hand that crude extracts of liver were inactive but that unsaponifiable fractions were active. His best fractions gave twelve sarcomas at the site of injection in fifty-six mice; Schabad's active extract produced four sarcomas in one hundred and seventy-nine mice, one hundred and eight of which had survived eight months.

Unfortunately, neither in the experiments of Steiner nor of Schabad is it easy to find whether they tested the extracts, saponified and unsaponified, from the same livers in each case.

Menke's carcinogenic preparations were crude fatty extracts of human breast cancer; where the unsaponifiable fraction was tested it proved inactive but the experimental data do not indicate whether saponification does indeed concentrate the carcinogenic factor. In experiments on the isolation of the active substances, Hieger found on fractionation of the unsaponifiable fraction of human cancer liver and non-cancer liver, lung, or muscle, that the carcinogens were concentrated in that fraction which was richest in cholesterol (about 85 per cent. cholesterol).

It will be recalled that Dickens (Dickens and Weil-Malherbe, 1945) found that cholesterol acts as

a tumour-promoter when it is added to a solution of a carcinogenic hydrocarbon, which would fit in well with some hypothesis such as : foreign fats are feebly carcinogenic when injected into sufficiently sensitive mice and the potency is increased in the presence of cholesterol. In the opinion of the writer, the investigation of feeble carcinogens will prove very difficult until some method is devised of overcoming the uncertainties due to inherent variations of susceptibility of the experimental animals. Until then it will be necessary to use large numbers of animals if it is attempted to make each group representative ; otherwise, contradictory results obtained in different laboratories can always be explained away by " susceptibility variations " of the experimental animals.

Carcinogenic Action of Heated Fats and Lipoids

Peacock's article is based on an examination of the thesis that the high incidence of gastric cancer in humans is due to a dietetic factor, namely the production of carcinogenic substances in food, especially fats, by overheating in the process of cooking, the critical temperature being in the region of 300° C.

He cites Kennaway's experiments with $AlCl_3$ and tetralin which reacts at 60° C. to give a complex carcinogenic mixture of compounds. The activity is concentrated in the high boiling fraction when the mixture is distilled, but it is surely incorrect to suggest that distillation at 270° C. yielded carcinogens which were not present in the undistilled mixture. The vivid fluorescence both before and after distillation is due to benzpyrene, which is concentrated in the high boiling fraction on distillation.

Peacock describes some interesting experiments where fowls were injected with dibenzanthracene in heated lard on one side of the body and with heated lard alone on the other ; 3 fowls developed tumours on both sides which suggested that dibenzanthracene was slowly removed from one side and stored up by the lard on the other side. No tumours resulted from the injection of heated lard alone into fowls. Burrows, Hieger, and Kennaway (1932) obtained twelve tumours, which were either sarcomas or fibromas, in 217 rats injected with lard alone. Much care was taken to reduce the chances of contamination by carcinogens ; but even now, 17 years after the experiments were carried out, the question of contamination is not completely settled. Lard which had been heated to 350° C. was also tested but the yield of tumours (two sarcomas) was, unfortunately for Peacock's thesis, reduced instead of increased by heating. It is not easy to interpret a passage in Peacock's paper dealing with " the minimal effective concentration of carcinogen," but probably what is meant is that carcinogen might be formed during overheating of fat but in amounts too small to be detected by biological methods. Recent work by the writer will throw a little light on the gloom surrounding the question of the minimum dose ; the record for the minimum is held by Shear, who produced a tumour in a mouse with 0·4γ dibenzanthracene dissolved in cholesterol. Chlosterol has been regarded by most investigators as non-carcinogenic (although no one has yet reported the results of tests with the pure sterol) ; however, some doubt must now be cast on the non-carcinogenic reputation of commercial cholesterol and therefore the 0·4γ must be multiplied an unknown number of times.

With regard to the feeding of overheated fats, Beck and Peacock (1941) induced gastro-papillomas but not carcinomas in rats fed with heated lard, although this condition can be brought about by a number of dietary deficiencies ; and a somewhat similar conclusion was arrived at by Morris, Larsen, and Lippincott, who fed rats with a diet containing 50 per cent. of lard heated to 300° F. for half an hour and found gastric ulcers and fatty degeneration of the liver.

The possibility of co-carcinogens promoting the effect of sub-threshold doses of carcinogen in the diet is still under consideration.

Peacock thinks it possible that the endogenic carcinogens are in part of exogenic origin and are found in the liver because they enter the body with the food and are carried along the metabolic route to be dissolved in the fat of the liver. There is certainly something attractive about this idea, for it would explain the haphazard distribution of liver carcinogens on individual dietetic differences, and also it would explain the age incidence of cancer since it would be expected that the carcinogen would gradually be accumulated during life. Against the theory is the fact that lung, kidney, and muscle of cancerous and non-cancerous subjects contain " endogenic " carcinogen, that the livers of newborn children contain it, and that in Europeans liver cancer is only about 1 per cent. of all carcinoma.

Peacock summarizes the experiments on the carcinogenicity of heated fats in a table (Table 4).

Oestrogens and Neoplasia

The extraordinarily interesting paper by Burrows and Horning suggests that the sex hormones form an essential part of the structure or mechanism or both, of numerous tissues of the body and that variations whether excess or deprivation upsets the normal development of the tissue. Whether the

TABLE 4

PEACOCK'S SUMMARY OF EXPERIMENTS ON THE CARCINOGENICITY OF HEATED FATS

Author	Substance	Temperature and time of heating	Method of administration	Yield of tumours*	Nature of tumour
Beck (1941)	Cotton-seed oil	340°–360° C. 1 hr.	0·5 ml. subcutaneously	(12) 2/6	Spindle-cell sarcomas after 414 and 538 days
	Cotton-seed oil	200°–220° C. 12 hrs.	0·5 ml. subcutaneously	(12) 0/3	—
	Cotton-seed oil	Unheated	0·5 ml. subcutaneously	(12) 0/10	—
Beck, Kirby, and Peacock (1945)	20% chlosterol in olive oil or cotton-seed oil	270°–300° C. ½ hr.	0·5 ml. subcutaneously	(18) 1/8	Spindle-cell sarcoma after 386 days
	20% chlosterol in cotton-seed oil	270°–300° C. ½ hr.	Painted	(12) 0/12	—
	Residue from heated cholesterol, 20% in olive oil	270°–300° C. ½ hr.	0·5 ml. subcutaneously	(12) 1/11	Spindle-cell sarcoma after 345 days
	20% chlosterol stearate in arachis oil	300° C. ½ hr.	0·5 ml. subcutaneously	(18) 0/18	—
	25% cholesterol palmitate in arachis oil	300° C. ½ hr.	0·5 ml. subcutaneously	(24) 0/24	—
	20% cholesterol in arachis oil	430° C. ½ hr.	0·5 ml. subcutaneously	(18) 0/18	—
	17% cholesterol in acetone	430° C. 1 hr.	Painted	(18) 3/4	2 regressing 1 persistent papilloma; earliest 460 days

* The numbers in brackets give the initial numbers of mice under test. Fractions give the ratio of tumours to animals surviving at the time of the first tumour's appearance.

fate of these tissues is neoplastic change or not, the most obvious influences are to be found in the female generative system and in analogous tissues in the male.

The cells of the pituitary, the master organ of the body, respond to œstrogen by changes in the proportion of chromophile or chromophobe cells and may even become hyperplastic or adenomatous. Mice, rats, and other rodents treated for prolonged periods with œstrogen showed great enlargement of the pituitary; in Burrows' experiments the pituitary would sometimes occupy one-third of the cranial cavity. However, stoppage of the supply of œstrogen caused the pituitary gradually to resume its original size, and the overgrowth could be reversed or even inhibited from the beginning by the injection of thyrotropic hormone.

Artificial as well as natural œstrogens have been reported as stimulating different types of cells in the pituitary, and the various strains of mice react differently to equal doses of the hormone.

The hamster shows great sensitiveness to pituitary tumour promotion by œstrogens, especially if thiourea is given simultaneously.

The ovaries had long been thought to play an important role in the development of breast cancer before experimental proof was obtained by prevention of the disease in mice by early ovariectomy and the re-establishment of the conditions for breast cancer by the injection of œstrogen, and moreover, by the incidence of breast cancer in male mice of liable strains by treatment with large doses of the hormone.

The genic factor in mammary cancer in the mouse has now given place in importance to extra-chromosomal influences and to the dominating effect of œstrogens. The maternal factor is transmitted in the milk but can be extracted from blood, spleen, and thymus; and evidence continues to accumulate that it is a virus for it has the appropriate physical properties and it multiplies in the host from generation to generation.

The experimental induction of uterine fibroids in mammals by œstrogens has been confirmed by many investigators. The guinea-pig is specially susceptible, and here ovariectomy had been reported as accelerating the appearance of the tumours; in one series of experiments the latent period was only thirty-two days, and it has been shown that, just as in pituitary adenomata, regression occurs if the treatment is stopped, for example, by removing the pellets of œstrogen from the uterus.

The pituitary is not involved in the production of uterine tumours by œstrogen, for hypophysectomized guinea-pigs still respond to treatment with œstrogen; androgens or progesterone act as inhibitors to the œstrogen.

The results of clinical experience bear out laboratory tests on animals, for uterine fibroids, and functional menorrhagia are now known to be associated with a high level of œstrogen in the circulation. In human subjects öophorectomy or chemical inhibitors (testosterone) causes the tumours to regress. The authors emphasize that care must be taken with the administration of hormones affecting the uterine tissues, especially as malignant and benign tumours of the uterus sometimes react differently.

Carcinoma of the uterus in mice can be produced by œstrogens provided the appropriate strain is chosen for the experiment; Allen and Gardner (1941), working with the CBA strain or with CBAxC57 crosses, found that uterine carcinoma arose in over 50 per cent. of the animals by as low a dose as 16·6γ of œstradiol benzoate given weekly.

The association of uterine adenoma and adenocarcinoma with other lesions known to be due to excessive œstrogen activity, for example, fibroids, polypoid adenoma, endometrial hyperplasia, and carcinoma—which are sometimes all found in the same patient—suggest that the same cause is responsible.

Oestrogens acting on the testis in mice cause hyperplasia of the Leydig tissue, particularly in Strong A strain mice, and finally evoke interstitial testicular tumours.

The two types of tissue in the prostate are differently stimulated by the sex hormones; excess œstrogen causes hyperplasia of the fibromuscular stroma in the prostate of the guinea-pig and atrophy of the secretory elements, which can be checked or prevented by progesterone, desoxycorticosterone, or testosterone. Thus the benign enlargement of the prostate in elderly men is thought to be due to a decline in the secretion of the inhibitory sex hormones relative to the supply of œstrogen.

After it had been observed clinically that an excess of œstrogen and androgen was excreted in the urine of patients suffering from adrenal tumours, Wooley, Fekete, and Little (1939) experimentally obtained nodular hypertrophy of the adrenal cortex by ovariectomizing mice; Gardner found 80 per cent. of adrenal cortical tumours in ovariectomized mice of the NH strain.

The CE strain of mice is highly susceptible to adrenal tumours, for 100 per cent. develop adrenal carcinoma after ovariectomy or castration shortly after birth. The tumour-bearing mice show all the histological changes in the accessory sex organs characteristic of prolonged stimulation with œstrogen, and it has been suggested that the adrenal in these cases is attempting to compensate for the loss of the gonads by over-production of hormone.

Local sarcomata, both spindle-celled and round-celled, have been obtained by several investigators who repeatedly injected mice and rats subcutaneously with œstrogens. The carcinogenic potency is of course much lower than that of the hydrocarbons, but there is little doubt that it can be demonstrated. Lacassagne has reported a very high percentage of local sarcoma in mice injected with testosterone.

The carcinogenic hydrocarbons show slight œstrogenic activity, and from this fact it is deduced that the two properties overlap, but of course the œstrogens are hundreds if not thousands of times more potent than the hydrocarbons and to speak of overlapping is somewhat academic.

Oestrogens are now thought to play an important part in the induction of leukæmic conditions in the mouse; Gardner and others (1940, 1944) have increased the incidence of lymphoid tumours in a low leukæmic strain of mouse from 2 per cent. to 25 per cent. by œstrogen administration, and have found evidence of the antagonistic action of androgen and œstrogen.

Some interesting experiments of Dmochowski and Horning indicate that the induction of leukæmia and of mammary cancer in the mouse show certain similarities in that a long latent period can elapse between treatment with œstrogen, which rapidly produces some permanent change in lymphoid or mammary tissue, and the development, several months later, of neoplastic changes.

To add to the catalogue of the biological activities of œstrogens, it has been found that they cause new bone formation on injection into immature female rodents; the medullary cavities of the long bones may become almost solid and there has been observed a sex incidence of bone tumours in liable strains of mice, where 77 per cent. of the tumours occur in the females and 29 per cent. in the males and at a later stage.

The formulæ of some compounds of interest in this field are shown in fig. 31.

Carcinogenic Action of Stilbene Derivatives

The theme of Dodds' short article is that, for compounds consisting of condensed benzene rings, All were tested by "the standard method" for carcinogenic action, that is, by painting on the skin of the mouse. Surely another procedure, namely subcutaneous injection, can equally be called the standard method and in many ways it is more sensitive and precise than dabbing a drop of solution

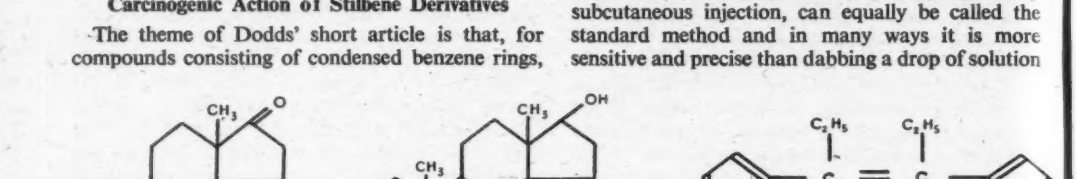


FIG. 31.—Oestrone (left); testosterone (centre); stilboestrol (right).

analogues exist with similar biological activity but with the difference that some of the rings are opened and substituted by short chains; by a little adjustment on paper the rings can be re-constituted to give back the polycyclic aromatic compounds.

As the leading example of the idea ("merely a hypothesis") the structure of œstrone and stilboestrol

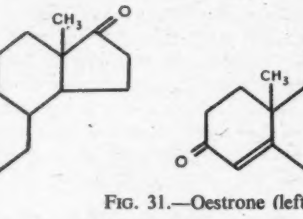


FIG. 32.—Oestrone.

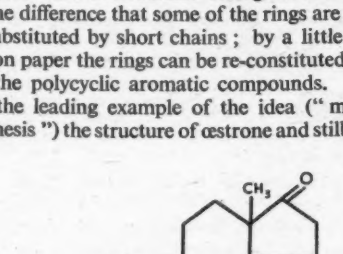


FIG. 33.—Stilboestrol.

are given in figs. 32, 33. The formulæ show that to pass from œstrone to stilboestrol would necessitate (1) introduction of an ethylene bridge; (2) removal of CH_3; (3) substitution of an aromatic benzene ring for a substituted penta ring; and (4) opening of the two closed rings.

Six compounds containing open rings have been tested which show a close relation, on paper, to the best known carcinogens; for example, for benzpyrene, the analogue was α-ethyl-β-sec-butylstilbene (figs. 34, 35), and similarly for 1 : 2 : 5 : 6-dibenzanthracene; for 3 : 4-benzphenanthrene, etc.

on approximately the same site of a somewhat restless mouse.

Of six analogues tested on 350 mice, only one compound produced tumours (α-ethyl-β-sec-butylstilbene) in two mice, and the tumours are described as a spindle-celled carcinoma and a spindle-celled sarcoma, which suggests that the

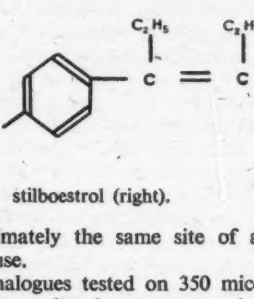


FIG. 34.—3 : 4-Benzpyrene.

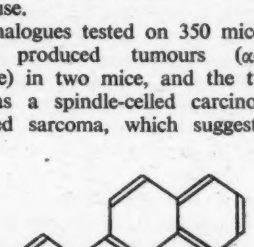


FIG. 35.—α-ethyl-β-sec-butylstilbene.

carcinogen might have given more positive results if the test had been made on connective tissue.

The last paragraph of Dodds' article runs:

"In conclusion, it would appear that these substances have little interest from the point of view of experimental cancer production, since the experimenter has the choice of a large number of compounds of an infinitely greater potency. The interest in them is therefore purely theoretical, in that it does seem to support the hypothesis that simple analogues can be prepared for a number of the complex condensed carbon-ring compounds, including the carcinogens."

However, since the experimental data show that open-ring analogues do not exhibit the biological activities of closed-ring hydrocarbons, by inference stilboestrol is œstrogenic not because it is an analogue of œstrone but for some unknown reason.

Experimental Cancer of the Bladder

Bonser's survey of cancer of the bladder begins with an account of the repeated attempts to reproduce in the laboratory the disease occurring in workmen in the dye industry, where they are exposed to dye intermediates like aniline, α-and β-naphthylamine, and benzidine.

Hueper and others (1938) were probably the first to succeed, for in the search for some experimental animal which would respond they found that large doses of β-naphthylamine given orally to dogs (300–450 mg. daily for twenty to thirty-two months) caused papillomatosis and carcinomatosis in twelve of sixteen animals. Bonser treated dogs with specially purified β-naphthylamine and confirmed Hueper's findings that species differences in the experimental animals are of importance; she was unable to induce bladder tumours in CBA mice using β-naphthylamine, although mice of this strain are very liable to bladder cancer when injected with the versatile carcinogen, 2-acetylaminofluorine. Wilson, De Eds, and Cox (1941) found in 1941 that it could evoke carcinoma of the bladder and other organs in a large proportion of albino rats of the Slonaker colony, but Wistar rats did not react in the same way; when the acetyl compound was tested on five different strains of mice all gave some bladder tumours, and in 18 CBA strain mice fourteen tumours arose, 86 per cent. of which were malignant.

Not only are dye intermediates (that is, aromatic amines) carcinogenic for the bladder in animals, but also the finished products themselves when these are given orally. The Japanese workers have been prominent in this branch of the subject; Yoshida in 1935 reported bladder papillomata in thirty-six of 168 rats fed with o-aminoazotoluene and Otsuka and Nagao also described bladder papillomas in thirteen of thirty rats fed with o-m'-dimethylazobenzene. In an attempt to see whether the effect of the carcinogen is via the urine, Berenblum and Bonser, using mice, examined the effect of the urine of workers from a dye factory, but with negative results.

Strömbeck made grafts of pieces of rat bladder epithelium into the livers of other rats which were fed with a diet of rice flour and azotoluene. A proportion of the intact bladders became papillomatous and hyperkeratotic, while the grafts remained free from metaplasia or papillomas, showing that the origin of the tumours was urogenous rather than hæmatogenous.

Carcinogenic Action of 2-Acetylaminofluorene

This carcinogen (AAF) (fig. 36) has the peculiarity of inducing tumours in a number of organs and tissues when it is added to the diet of animals such as the mouse, rat, fowl, and cat. Bielschowsky, using rats, found that they tolerated 4 mg. per day, which produced numerous neoplasms nearly all of epithelial origin; leukæmia and mesodermal tumours were rare, for only one uterine sarcoma arose in five hundred rats. In the head were found squamous keratinizing carcinomata of the ductus acusticus externus, and carcinomata of the eyelid originated in glandular structures; in the neck adenocarcinoma of the thyroid, and in stimulated hyperplastic thyroids malignant tumours, could be produced. Basal-celled carcinoma arose in the skin and mammary cancer in the breast, more frequently in Wistar rats than in piebald rats, and in the thorax there were adenomata and metastasising cancer of the lung; in cats microscopic nodules in the lung developed where the normal tissue was replaced by squamous keratinising epithelium. In the abdomen, the liver, bladder, small intestine, colon, pancreas, stomach, and uterus have all more or less frequently responded to treatment with AAF.

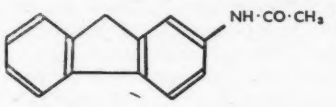


FIG. 36.—2-Acetylaminofluorene.

The genetic constitution and the age of the animal are important factors in the pathogenesis of these neoplasms. The combined administration of allylthiourea and AAF produced malignant tumours of the thyroid, and combined stilboestrol and AAF resulted in the growth of malignant tumours of the pituitary.

The tumours of the liver were very similar to those induced by another carcinogen, dimethylaminoazobenzene.

An analogous amine, 2-aminoanthracene which must be one of the very simplest carcinogens, was also found to be active, for it produced spindle-celled tumours of the skin in the rat.

Production of Liver Tumours by Azo Compounds

Orr's succinct article deals mainly with the carcinogenic action of p-dimethylaminoazobenzene

(butter yellow, DMAB) (fig. 37), and also with o-aminoazotoluene (AAT) (fig. 38), which was the first azo compound found to be effective in liver tumour production by Yoshida in 1932.

There is the usual tribute to organic chemical synthesis leading to the now familiar conclusion that no all-embracing co-relation can yet be made between chemical structure and carcinogenic potency, and there are also the facts about the susceptibility of species and strains of some experimental animals and the resistance of others.

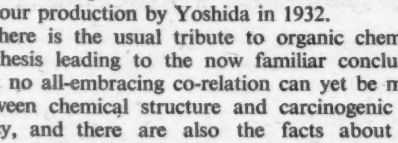


FIG. 37.—4-dimethylaminoazobenzene (" butter yellow").

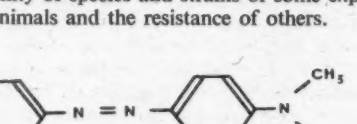


FIG. 38.—4'-animo-2 : 3'-azotoluene.

Some information about the administration and dosage of the two azo compounds would have been welcome.

Much work has been published on the effect of alterations in the diet although the results of such changes are difficult to explain.

Diets containing liver, kidney, rice, yeast, wheat flour, high levels of vitamin B, riboflavin, hydrogenated coconut oil, whole milk, and a high proportion of casein have all been reported as affording protection against liver carcinogenesis by azo compounds, but in some cases confirmation of the results by independent investigators could not be obtained.

Orr is scrupulously careful to quote both sides in controversies and such open mindedness will give satisfaction to the critical. For example, it is stated that (1) cirrhosis is frequently associated with subsequent hepatic carcinoma ; (2) tumours have been found in non-cirrhotic livers ; (3) cancer can develop at a stage when cirrhosis is reversible ; (4) cirrhosis can be induced by DMAB in rabbits but liver cancer is unknown in this species.

Histologically liver tumours consist largely of two types, liver-cell carcinoma or hepatoma, and bile-duct carcinoma or cholangioma. It has been argued that if the action on the bile duct cells is direct, it would be possible to find extra-hepatic bile-duct carcinoma. *In vitro* experiments on cultures of liver cells and bile-duct epithelium treated with N : N-dimethyl-p-phenylenediamine show that the liver cells are much the more sensitive, and the same applies to the tumours derived from these tissues. The reason for the conclusion that this difference is strong evidence in favour of the existence of bile-duct carcinoma is not altogether clear.

Metabolic studies show that in the glycolytic activity of the tumours the substrate is glucose, whereas normal liver cells utilize glycogen and do not attack glucose.

> " The fact that glucose-breakdown replaced glycogenolysis in the tumours was confirmed by Dickens and Weil-Malherbe (1943). They also investigated several highly-specialized functions of hepatic cells in the tumours, and found that the following were entirely, or almost entirely, lost : the formation of urea from ammonia or from l (+) -alanine, and of acetoacetic acid from caprylic acid ; the oxidation of uric acid ; and the synthesis of fermentable carbohydrate from pyruvic acid."
>
> " Woodward (1943) showed that the alkaline β-glycerophosphatase activity of DMAB tumours averaged ten times that of normal rat liver. Cohen (1945) found that, in rats receiving DMAB, the liver showed a progressively-decreasing glyoxalase activity ; tumours and their transplants showed about ten per cent of the glyoxalase activity of normal liver."

The mode of action of the azo carcinogens has been examined by a study of their split products which were found to be toxic to various enzymes, for example, a diphosphopyridine nucleotide system, carboxylase, and a sulphydryl containing enxyme (urease). One of the metabolites, p-benzoquinone, is powerfully inhibitory to carboxylase. The view has been proposed that, although it is itself non-carcinogenic, the quinone is continuously renewed at sensitive sites in the tissues when the parent compound (DMAB) is administered, and that detoxicating reactions never allow these sites to be reached by the quinone when it is itself given directly to the experimental animal.

Occupational Cutaneous Cancer Attributable to Certain Chemicals in Industry

Henry's fascinating account of pitch, tar, and oil cancer in workmen in industry is illustrated by selections from a classical collection of photographs of industrial processes which convey the atmosphere of authenticity by captions such as, " Females at slubbing frames in a cotton mill " or " Topman on a producer gas plant. Note position during prodding."

Historically, the study of industrial cancer was begun by Percival Pott in 1775, who had drawn

attention to soot as a cause of scrotal cancer, and by Butlin in 1892, who showed that other substances—pitch, tar, and mineral oil—similarly affected the same site. Between 1907 and 1920 the list of diseases which were covered by the Factories Act (Workmen's Compensation) included "epitheliomatous ulceration and cancer due to pitch, tar, bitumen, paraffin, and mineral oil, or any compound or residue of any of these substances or any products thereof."

Between 1920 and 1945 the number of notifiable cases of cutaneous epithelioma amounted to 3,753 (occurring in nearly 3,000 persons) of which pitch, tar, or tar products were held responsible for 2,229 (59·4 per cent.), and shale oil, mineral oil, or bitumen for 1,515 (40·3 per cent.). Without data on the size of the population exposed to these substances, little idea can be obtained of the incidence rate. Henry gives a graph of the induction time before the disease is detected; if frequency of incidence is plotted against time after commencement of employment, a steeple-shaped curve is obtained both for shale and mineral oils and for pitch, tar, and tar products, where the maximum number of cases in oil workers occurs after about fifty-two years and in pitch and tar workers after about twenty-two years. The shortest induction time for pitch and tar was ten months, and for oil four years.

Henry analyses in detailed tabular form the number of cases of cancer, occupation, site of the disease, and causal agent.

While the specialist in industrial cancer is chiefly interested in the statistical aspect of cancer incidence, he is also concerned with the application of the Compensation Act; and consequently Henry sometimes breaks off into a most interesting investigation of the occupational biography of a particular workman. For example:

> "The man in question used only a Trinidad-Lake bitumen for the purpose, and in a previous communication I suggested that this case could be attributed to bitumen after twenty-one years' employment; but further enquiry has now shown that he spent only just over two years in the special asphalt-trough department and that the previous nineteen years were occupied in cable-making, and so in contact with coal tar."

Again:

> "There was, however, also an important case of epithelioma of the forehead in one man who had been a clerk for twenty-three years only in the office adjacent to the factory in which the pitch-dust was generated."

and

> "Even a time-clerk for forty years and an ambulance room attendant were not exempt, but the latter had previously been a fitter on the plant; while the history of removal of a keratotic growth from the head of a managing director is, no doubt, of interest."

It is a sad yet logical fact that the sufferings of the victims of industrial cancer should have initiated the onslaught on the problem of cancer by chemical technique.

The Role of Arsenic in Carcinogenesis

Currie, in discussing arsenic cancer, shows that the evidence comes largely from the disease in human subjects, in miners exposed to dust containing arsenides, in sheep-dip workers, and in patients with psoriasis who have been treated with arsenicals.

The radioactivity of the dust in the Schneeberg mines has suggested that the radiation and not arsenic is the cause of lung cancer occurring among cobalt miners, but the typical hyperkeratosis of arsenic intoxication on the palm of the hand has been observed in the men who wash the cobalt ores.

Just as the Schneeberg lung cancers have been attributed to radioactivity and not to arsenic, so pitch, tar, and mineral-oil cancer has been suggested as due to arsenic (Bayet and Slosse, 1919) who attempted to identify some common cause of industrial cancer.

It has been found, however, that the minute arsenic content of different tars bears no relation to their carcinogenic potency, that coal miners show no higher incidence than the general population, and that the keratosis of the palms and soles are not typical of pitch, tar, or mineral-oil cancer. Scott also concluded that arsenic was not the cause of the cancers seen in workers who use shale oil although the keratosis of the skin in these workers shows some resemblance to the chronic arsenical condition.

The commonest pathological changes in the skin of the hands and feet in arsenicism are hyperpigmentation (or melanosis) and keratosis (which takes the form of corn-like elevations and occur in about 80 per cent. of the collected cases of arsenical skin cancer). In the great majority of 140 recorded cases the drug had been administered for a very long time, up to thirty years, but the high incidence in psoriatics treated medicinally has also been explained by a predisposition of the skin to cancer.

Kennaway's analysis of thirty-eight cases of arsenic cancer emphasizes that while in tar, pitch, and shale-oil cancer, the scrotum, head, and neck are the sites of election, in arsenic cancer 46 per cent. were located on fingers, legs, feet, toes, and trunk, 23 per cent. on arms and hands, 23 per cent. on scrotum, penis, head, face, neck, and eyelid, and 8 per cent. on other parts.

Some sixty-five cases of skin cancer have been reported from Cordoba in Argentina, where water

from some of the drinking wells was found on analysis to contain 0·45 mg. per cent. arsenic.

The re-production of arsenic cancer in experimental animals was accomplished by Leitch and Kennaway (1922), who found two tumours, one of them malignant, in two hundred mice which had been painted with potassium arsenite, and other investigators have induced sarcomatous changes in mice, chickens, and rabbits by parenteral injections.

Occupational Cancer of the Bladder

One of the longest articles in the *Bulletin* is Goldblatt's on cancer of the bladder in dye workers; seven and a half pages, more than half, will interest chiefly medically qualified readers, for it consists of a survey of factory medical control, the signs and symptoms of the disease, pathogenesis and pathology, treatment and surgery, and surgical prognosis.

Of the numerous compounds used in the dye industry, only a few have been definitely assigned a urogenous carcinogenic role; these are β-naphthylamine and benzidine, and probably aniline and α-naphthylamine; hydrazobenzene is regarded as a potential carcinogen since it can easily give rise to aniline.

These compounds represent intermediate stages in the synthesis of dyes, and in some cases these stages are numerous; but examination indicates that the majority of bladder cancers occur in the workmen who are engaged on the process where the incriminated compound is actually produced or used, although absorption must occur wherever contaminated objects are handled, such as in laundries and repair shops.

The fumes, vapours, and dust of the dangerous substances are breathed, penetrate the clothes and skin, and in the past were taken in with the food. Efforts have been made in recent years to protect the dye workers by enclosing the plant, by conveying the intermediates in pipe-lines and other mechanical devices, and by general hygienic regulations; but it is feared that some of the plant modifications and hygienic recommendations are as yet mere projects.

The bladder cancers now coming to hand were probably incurred at some time in the past, measured in decades, when it was considered more profitable to pay compensation than to redesign factory plant.

Experimental investigation with dye intermediates has been carried out on mice, rats, rabbits, monkeys, and dogs, in an attempt to reproduce bladder cancer in the laboratory; dogs responded to β-naphthylamine, but no animal tests have given positive results with benzidine, which is a potent carcinogen industrially. Such demonstrations of the difference in susceptibility of different species suggest that experimental evidence for the carcinogenic potency of dye intermediates is not an altogether satisfactory method of estimating toxicity for human subjects. Many of the compounds used in the dye industry, although not as yet known to be carcinogens, have a very harmful effect on the system, causing cyanosis, methæmaglobinæmia, and hæmorrhagic cystitis. These substances include "nitro compounds, amines, chloramines, nitroamines, phenols, diamines, chlor-nitro compounds, and derivatives of amides."

> "It would appear almost as if the excitation of tumour formation by bladder irritants requires the latter to be (*a*) of the less violent kind and (*b*) exhibited in doses insufficient to lead to acute symptoms. In general terms, the tissue requires opportunity and time to react to the carcinogen, whereas the violent bladder-irritants break down the tissue reaction in its earliest stages. One of the most striking characters of these tumours is the furtive manner in which they develop, and another that they can arise long after all obvious exposure to the presumed carcinogen has ceased. The tumour-forming process, nevertheless, is at some stage accompanied or preceded by evidence of instability of the lining membrane of the bladder (flaking-off of epithelial cells) and/or of inflammatory changes (leucocytes) in the urine."

Examination of the urine from the workmen or from experimental animals treated with the amines showed they are excreted as hydroxylated or acetylated derivatives or as compounds conjugated with sulphuric acid. Since phenols and acyl and aryl derivatives show no carcinogenic activity in workmen who are in contact with these substances, Goldblatt deduces that the amine itself, and not the hydroxyl, acetyl, or sulphuric acid derivative, is the effective carcinogen.

The latent period, that is, the interval between the first exposure to the carcinogenic compounds and the appearance of symptoms of the disease, was found by Goldblatt to be eleven to sixteen years in 54 per cent. of his cases, and twenty to forty-eight years in 19 per cent. Since the disease sometimes appears many years after occupational contact with the compounds has ceased, the period of exposure is different from the latent period. Here he found the shortest time was three and a half years and the longest thirty-three years, and in fifty-four cases 48 per cent. of the workmen had had three and a half to nineteen years in the industry and 13 per cent. had had twenty-six to thirty-three years.

In the dye workers, and also in experimental animals, the location of the tumour shows that they arise in those parts of the bladder which are exposed for the longest time to urine, and any decreased solubility of the amines and their metabolites owing

to an increased alkalinity would lead to an accumulation of undissolved matter at the base of the bladder. Opinion is not yet unanimous on the question of whether the carcinogenic action is exerted by the dyes when they are in the urine or when they are still in the circulating blood. Goldblatt puts forward the speculation that two separate factors are concerned in bladder cancer, the endogenic factor and the "carcinogenic potentiator," that is, the amino compound.

The evidence advances in favour of this view are that carcinogens have been extracted from the urine of human subjects who were not dye workers (Steiner) and that location and histological characteristics show no fundamental differences between occupational and non-occupational bladder tumours. It is doubtful however, if such speculations without adequate factual support are very helpful. Goldblatt states :

> "The presumption is that the carcinogen is present in greater or lesser degree in all, but that the tumour reaction will depend on the sufficiency of the carcinogen or on that of the potentiator. Such a hypothesis could perhaps account for the marked tendency to "recurrence"—i.e., once potentiated, always potentiated.
>
> "Again, different individuals may be held to have varying amounts and availability of carcinogen and hence, even with the same amount of potentiation, varying response from none to extreme malignancy. (This is, of course, known among workers in aminobases.) The relative incidence of occupational bladder-tumours among young adults is much in excess of that of non-occupational tumours. This fact, on the above hypothesis, may be due to a marked potentiation of otherwise unsufficiently active carcinogen."
>
> "The problem is clearly more subtle. The key lies, we suggest, in discovering first what structural or functional changes are brought about in the bladder epithelium by the presence of the amino-bases or their derivatives. One of the changes brought about, already referred to, is a disruption of the stability of the layers of epithelial cells.
>
> The second necessary point to elucidate is the endogenous factor which, acting upon an epithelium which is attempting to regenerate, produces that extra stimulus which in the issue is carcinogenesis."

Goldblatt's article gives little idea of the incidence of bladder cancer in dye workers in relation to the number of workers at risk : there is not even some simple table of the number of annual cases. A variety of reasons contribute to this lacuna ; in the first place, the disease is not a notifiable industrial disease in Britain ; secondly, the time of onset is very difficult to determine ; thirdly, the absolute incidence of bladder cancer in the general population is considerable ; and, finally, it has been found impossible to estimate the number of workers in the dye industry who are actually exposed to the dangerous substances.

However, Hueper, in *Occupational Tumours and Allied Diseases* (1942), states that in small groups of workmen who receive continuous and massive doses of bladder carcinogens the frequency of the disease may be as high as 80 to 90 per cent., that investigators have found the cancer incidence to vary in different factories from 0·4 to 20 per cent., and that it has been reported that in Basel bladder cancer is thirty-three times as common in dye-workers as in the general male population.

Chemotherapy of Cancer

Haddow begins his discussion with a note on the history of cancer therapy by drugs in the last 1,500 years, when belladonna, aconite, mercury, antimony, and arsenic were all used, especially arsenic, which was still applied to chimney sweeps' cancer in the middle of the last century. The early therapists had every reason to be alive to the difficulties of the task, which has been made clearer today by the realization that the differences between normal and neoplastic tissue are almost too subtle to be revealed even by immunological characteristics ; it is as though the mechanisms are different but the protein structures have been only slightly modified.

Haddow advances the revolutionary idea that a drug for cancer therapy which could selectively inhibit or kill cancer cells might undo the carcinogenic process and thus, by reversing the chain of events, drive back the cancer cells to differentiation and normality. Unfortunately, no evidence yet exists which might suggest that such reversal is possible.

At the present time, three types of chemical substances have been found to be of benefit in inhibiting tumours ; these are : the œstrogens, used in cancer of the prostate ; the chlorethylamines, used in Hodgkin's disease and other lymphadenopathies ; and urethane, used in leukæmias. Treatment with œstrogens has so much in common with castration that Haddow devotes a passage to the results of the surgical method of treatment ; elsewhere, œstrogen therapy has been called "chemical castration."

Huggins, who is the authority in this field, found that in forty-five cases of advanced prostatic cancer treatment by bilateral orchidectomy caused sustained inhibition of the disease in thirty-one for thirty months ; in nine there was a temporary improvement, and five showed no change.

In 1940, Kahle and Maltry published results of the treatment with stilboestrol of fourteen cases of prostatic hypertrophy, seven of which had also drainage operations. In all these cases there was

relief of symptoms of obstruction, and in 1942 Kahle and others reported on seven cases of carcinoma of the prostate which had been successfully treated with stilboestrol for two years. Kearns, in 1941, had found that thirty-seven patients with carcinoma of the prostate who had received œstrogens showed :

> " . . . remarkable clinical amelioration, with gain in weight, relief of pain, improvement in blood-picture, slowing of sedimentation-rate, an approach to normal in the phosphatase estimations, retardation of growth in the skeletal metastases, with diminution in size and reduction of the nodularity and fixation of the prostate itself."

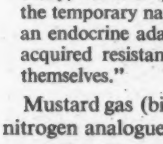
Haddow early in the development of the subject had treated a case of prostatic cancer with œstrogens and found improvement of the general condition ; and, although radiography did not give evidence of changes in the skeletal deposits, the patient is alive and well six years later. Haddow concludes that :

> " No evidence exists that carcinoma of the prostate can be cured by the use of œstrogens, but there is equally little doubt that under this form of therapy the foci of the disease may become quiescent, that life can be prolonged, and that temporary rehabilitation can be achieved."

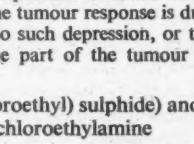
With regard to the mode of action of the œstrogens upon cancer of the prostate, there are a number of possibilities, for example, that there is a direct effect upon the prostatic epithelium via an inactivation of androgens, or by depression of the gonadotropic agents of the anterior pituitary, or by suppression of the activity of the interstitial cells of the testis. The malignant cells owe their sensitiveness to œstrogens to the retention of some physiological properties of the parent tissue. Haddow treated seventy-three cases of advanced cancer with synthetic œstrogens and found that in fifteen of thirty-six breast cases there was a significant but temporary retardation, and in thirty cases of cancer of other organs two responded by undoubted partial regression of the tumour.

> " It is, of course, likely that such relatively massive doses of œstrogens depress the pituitary and hence the ovary, but it is specially important to decide whether the temporary nature of the tumour response is due to an endocrine adaptation to such depression, or to an acquired resistance on the part of the tumour cells themselves."

Mustard gas (bis (β-chloroethyl) sulphide) and the nitrogen analogue, i.e., β-chloroethylamine



bis (β-chloroethyl) sulphide



bis (β-chloroethyl) amine

have not only a contact vesicant action on tissue but can also show profound cytotoxic effects, especially on tissues which are in active proliferation.

> " For both sulphur and nitrogen-mustards, this relatively specific cytotoxic action upon growing tissues is an outstanding pharmacological property, and after adequate doses affects the bone-marrow in the production of leucopenia, thrombocytopenia and anæmia, the intestinal tract in the production of diarrhœa and vomiting, and lymphoid tissues generally in the appearance of persistent lymphatic atrophy. In attempts to ascertain the cytological basis of such effects, it has become clear that the mitotic activity of a variety of cells from unicellular, invertebrate, amphibian, mammalian and plant forms is highly sensitive to inhibition by mustard gas and the chloroethylamines."

Mustard gas greatly increases the spontaneous mutation rate of drosophila and of neurospora. The biological action of the nitrogen mustards is believed to be due to the interaction of the cyclysed form with some tissue constituent :

> " . . . the capacity of ethylenesulphonium or imonium compounds to alkylate such functional groups as various amino-, imino, imidazole, sulphydryl, sulphide and phenolic groups of amino acids and peptides ; inorganic phosphate, glycerophosphate and hexose phosphates ; the amino groups of adenosine and thiamine ; the pyridino-N of nicotinic acid amide and pyridoxine ; and the carboxyl and amino groups of numerous proteins."

Mustard gas also attacks some enzyme systems. For example :

> " In a long list of enzyme-systems of which the sensitivity has been determined, the majority proved either resistant or to be only moderately inhibited, but among the most highly sensitive systems are hexokinase, creatine and pyruvate phosphokinase, inorganic pyrophosphatase, adenylic acid deaminase, and cholinesterase."

However, mitotic changes can be produced by concentrations of the drug which are too low to affect respiration or glycolysis, and in experiments on transplantable tumours it has been found that the cells have been killed or at least made non-transplantable without showing morphological damage.

The nitrogen mustards were first tested clinically for chemotherapeutic effect in 1946, when encouraging results were seen in Hodgkin's disease ; but in acute leukæmia, multiple myeloma, and myelogenous leukæmia the response was disappointing.

Lefèvre in 1939 had found that the mitotic effects induced by colchicine could be reproduced by phenylurethane, and Haddow and Sexton in 1946 showed that this compound was poisonous for the cells of the Lieberkuhn crypts in mouse intestine,

that it retarded the growth of spontaneous mammary cancer and transplantable rat carcinoma, and, moreover, that urethane itself gave the same results.

The effect on the rat tumour was found to be "accompanied by a profound modification in the histological structure of the tumour, the characteristic cellular structure giving place to a more fibrous structure with an abundant stroma, and indicating a change in the direction of increased differentiation."

Urethane was tested on cases of breast carcinoma and other types of cancer, but the only promising results were obtained in leukæmia, where :

> "Urethane does, in fact, produce remarkable changes in leukæmia, represented in the most favourable cases by a fall in total leucocyte-count to normal limits, a tendency for the differential count to approach a more normal pattern, diminution in the size of the spleen and enlarged lymph-nodes, and a rise in hæmoglobin level. There is a striking similarity between the leucocyte responses and those brought about by *x*-ray therapy. There is, however, no indication that permanent benefit may result from the use of urethane in either myeloid or lymphatic leukæmia, since relapses take place, immature cells may reappear in the blood, and all these changes are essentially reversible."

It was observed that various leukæmias in the rat and mouse were refractory to the action of urethane and thus the clinical test demonstrated species differences which could not have been predicted.

$$NH_2{\cdot}CO{\cdot}OC_2H_5$$

urethane (ethyl carbamate)

The investigation of the mode of action of urethane has followed the conventional pattern, namely, tests on analogues of urethane, and the effect on tissues and tissue constituents such as enzymes.

Warburg (1910) had recorded that the narcotic action of phenylurethane inhibited cell division, and later he found that the dehydrogenases were similarly influenced ; but here again the concentrations required to induce narcosis or to suppress growth are much smaller than those required for enzyme inhibition. Keilin and Hartree (1939) concluded from a study of the components of the cytochrome enzyme system that urethane renders an essential part of the respiratory mechanism inaccessible to oxygen. Other investigators have suggested that urethane has an affinity for some special component of the cell or that it competes with a natural amine which is essential for the synthesis of nucleotides.

Urethane, colchicine, and also arsenic have in common the property of inhibiting mitosis, and they also have a retarding influence on leukæmia.

> "It is an important problem whether the primary action of urethane is upon the growth-mechanism or upon differentiation-processes—to the extent that the two are separable. At the present moment one regards the latter as more likely, and can only suggest that the drug may act on growth primarily through the processes of maturation, and in leukæmia by tending to remedy some deficiency in these processes."

It is only too clear that the chemotherapeutic treatment for cancer is still in its infancy.

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FLUCTUATING ATMOSPHERIC PRESSURES

A NOVEL ENVIRONMENTAL VARIANT OBSERVED IN SUBMARINES

BY

F. P. ELLIS

From the Royal Navy

(RECEIVED FOR PUBLICATION, JUNE, 1948)

The need has been stressed in recent years for relating the design of fighting equipment to the physiological characteristics of the men who must be responsible eventually for its operation, as well as to its mechanical efficiency. Changes in environment may also affect mental or physical performance of a given task or interfere in other ways with physical well-being. The most widely known example is probably that of the airman, who has to contend with rarefied atmospheres, high accelerations, and sudden fluctuations in atmospheric pressure or in the thermal conditions to which he is exposed. The study of aviation medicine and physiology has arisen from the dual needs for designing aviation equipment and aircraft to meet the physical and physiological requirements and limitations of the air crew, and for selecting and training air crew to combat effectively the environmental stresses to which they are exposed.

The changes in environment encountered in submarines are of less violent degree, but in the past, nevertheless, certain avoidable hardships have been accepted as part of the day's work by the submarine sailor, and the need for providing him with an optimal environment is still less generally appreciated than in the case of air crew. The introduction of the "snort" or "schnorkel" to British submarines, to which references were made in both Houses on March 8, 1948, and in the press following the tropical and arctic cruises of H.M. Submarines *Alliance* and *Ambush*, led to a review by the Admiralty of the human factors which are related to the design and operation of modern submarines.

Continuous underwater activity was limited until comparatively recently by the capacity of the batteries to drive the motors which propelled the submarine underwater, and by the ability of the crew to remain efficient in an atmosphere which was steadily depleted of oxygen and to which carbon dioxide was constantly added by the respiratory processes of the crew. The batteries were charged at intervals by running the diesel engines with the submarine proceeding on the surface, an unhealthy procedure in close proximity to the enemy. The control of the latter factor was achieved during long dives by releasing oxygen when necessary from cylinders or generators, and by removing carbon dioxide with chemical absorbents.

The Netherlands Navy made a considerable advance just before the 1939–45 war when they fitted to their submarines a hollow extensible mast which enabled air for the engines to be conveyed to the submarine whilst it lay submerged, so that the batteries could be charged without obviously disclosing the whereabouts of the submarine. This idea was further developed by the Germans after they captured Dutch submarines in the invasion of Holland, and during the last two years of the war it was incorporated in U-boat design in the form of the "schnorkel," to enable operations to be continued in the face of steadily increasing opposition from Allied air and surface craft equipped with radar. The device proved successful; not only could the batteries be charged in greater safety than previously, but useful underwater speeds were achieved as well. The use of the "schnorkel" in British submarines was investigated in the early years of the war, but the idea was temporarily shelved, and then tried again in 1944.

The German "schnorkel" or British "snort" consists of a hollow mast which can be raised or lowered and connects the interior of a submerged submarine with the ambient air above the surface of the sea. Flooding of the submarine is prevented by a float-operated valve at the upper end of the mast. The mast contains an induction pipe through which air is drawn into the submarine, and an exhaust pipe through which the exhaust gases pass to an outlet a few feet below the inlet to the schnorkel induction, where the gases bubble out below the surface of the sea.

The resistance offered by the long narrow induction pipe to the heavy fresh air requirements of the engines causes a depression of the pressure within the submarine to varying degrees below one atmosphere when the engines are running. The extent of this depression varies in relation to the total revolutions registered by the two main engines, irrespective of whether the engines are being used to charge the batteries, to propel the submarine, or for both purposes. Fluctuations in the internal pressure are related to the state of the sea and swell, which in choppy or rough weather may occlude the air inlet temporarily with water shipped in-board or may close the float valve for short periods during which the engines draw upon the air in the submarine for their requirements ; and to the skill of the men and the efficiency of the equipment which maintain the submarine at a constant depth beneath the surface when snorting and so keep the snort inlet above water.

An opportunity for examining the nature of the pressure variations and certain related chemical changes in the atmosphere arose during an early " snorting " cruise in temperate waters in a British submarine which proceeded on the main engines and the snort by day, and at greater depths on the motors with the snort lowered in the hours of darkness.

Pressure Measurements

The tracings shown in fig. 1 were selected from records made during approximately 400 hours snorting with three barographs which furnished 9-inch horizontal tracings of the pressure variations over 7-day, 10-hour, and 2-hour periods respectively. On each " 7-day tracing " the corresponding total engine revolutions are indicated, and the average state of the sea and swell for the period under review is shown by the Douglas Scale as estimated through the periscope by the officer of the watch. (See footnote to fig. 1.)

In fig. 3 pressure fluctuations of unusual severity recorded early on in the trial are shown on a tracing from the " 2-hour " barograph, and by two tracings from a large barograph which recorded pressure changes over a " 10-minute " period.

In order to avoid confusion which might arise from the various terms in use for describing pressures, such as millibars, millimetres of mercury, inches of mercury, or pounds per square inch, the pressure changes are shown here as percentages of one atmosphere, and the aircraft heights at which reduced pressures of similar degree would be experienced are given to facilitate comparison between the two situations.

Chemical Measurements

The partial pressure of oxygen in the air of the submarine was indicated continuously on a Pauling Meter, a direct reading instrument designed in the United States, which depends on the paramagnetic properties of oxygen as opposed to the diamagnetic properties of most other gases.

When the snort mast was lowered and fresh air ventilation was impractical the percentage of carbon dioxide in the air was measured with an indicator of new design, which depends on the differing thermal conductivities of air samples of different chemical composition. The percentage of carbon dioxide in the air is shown on a galvanometer which indicates the difference in heat loss from two hot wires, one of which is exposed to compartment air saturated with water vapour from which carbon dioxide has been removed by a chemical absorbent, whilst the other is exposed to saturated compartment air from which carbon dioxide has not been removed. The accuracies of these instruments under laboratory conditions correspond reasonably closely with measurements obtained with the Haldane Gas Analysis Apparatus. Each time the instruments were read the atmospheric pressure was noted on a large aneroid barometer which had been calibrated against a mercury column before sailing.

Typical changes in the chemical composition of the air during a 24-hour period on Day 20 are shown in fig. 2. Horizontal lines indicate the partial pressures which correspond to 18 per cent. oxygen and 3 per cent. carbon dioxide at a pressure of one atmosphere, which have been suggested as permissible lower and upper limiting levels for these gases in compartments which must be occupied for prolonged periods.

Traces of carbon monoxide, occasionally caused by back pressure on the underwater exhaust during unexpected submergence with the engines running, or with a following wind from exhaust gases drawn in through the snort induction, were estimated with the Chemical Carbon Monoxide Indicator Mk. III developed at the Royal Aircraft Establishment, Farnborough.

Pressure Changes

The range of the pressure changes experienced on this trial is shown in figures 1A to 1D by records selected from tracings on the " 7-day " barograph. Varying degrees of pressure depression below one atmosphere were the main feature when snorting, and when submerged with the snort mast lowered, mild degrees of pressure elevation above one atmosphere were observed due to high pressure air leakages within the submarine.

The marked fluctuations in figs. 1A and 1E were due to slow speeds and low engine revolutions in a choppy sea before the crew were fully accustomed to the controls.

In fig. 1B the relationship between the pressure variations and the total engine revolutions may be observed, and an increase in the amplitude of the fluctuations may be seen when the sea and swell increased on Day 13.

In fig. 1C higher total engine revolutions and faster speeds are related to further depression of the atmospheric pressure to between 85 and 75

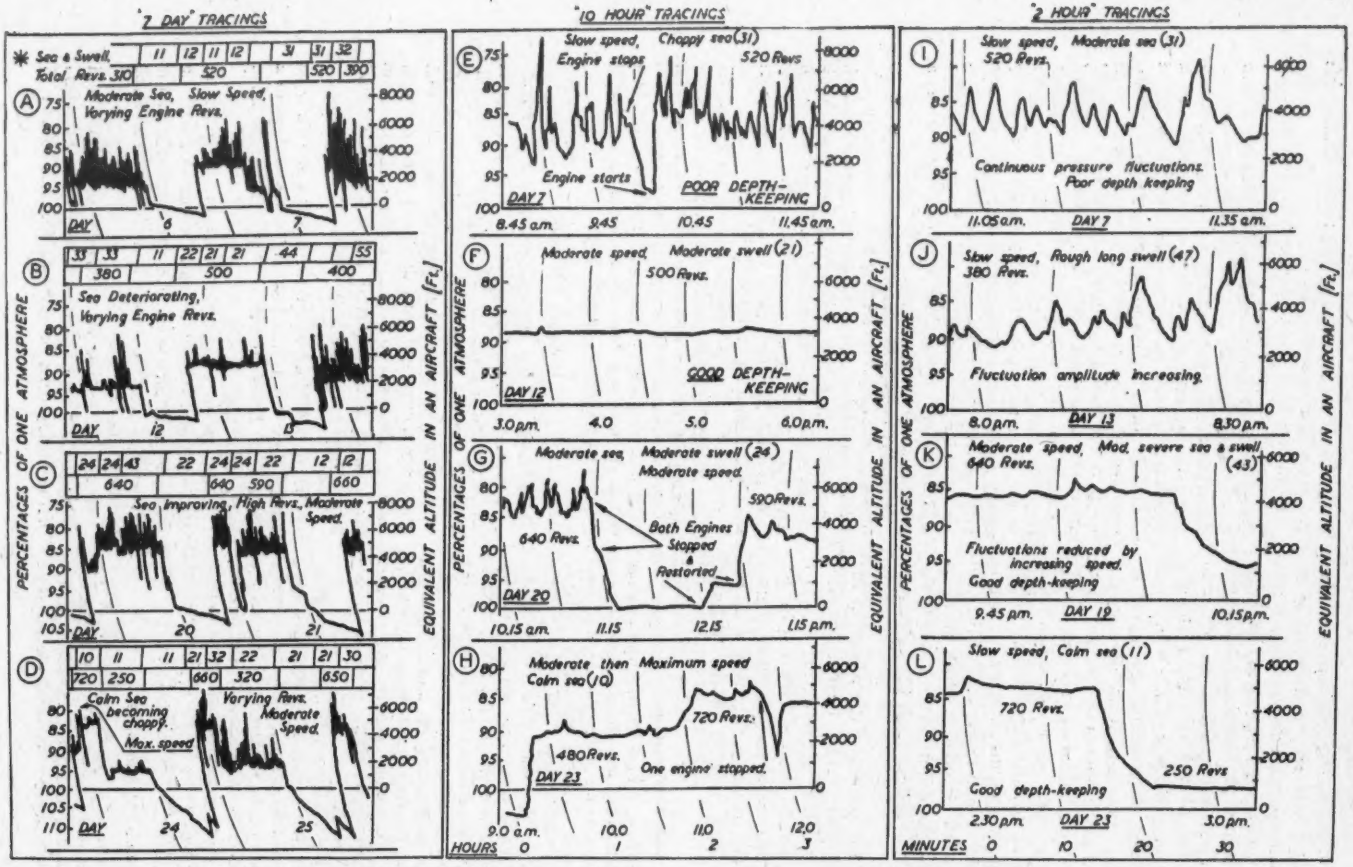

FIG. 1.—Variations in the atmospheric pressure within a snorting submarine.

DOUGLAS SEA AND SWELL SCALE

The first figure gives a numerical estimate of the state of the sea, and the second refers to the length and height of the swell. Increases in the roughness of the sea, or in the length and height of the swell, are estimated in each case by figures increasing from 0–9. Thus a flat calm would be 00, moderate sea and swell 33, etc.

PRESSURE EQUIVALENTS

Percentages of 1 atmosphere ..	70	80	90	100	110	120
Inches of mercury	20·9	23·9	26·9	29·9	32·9	35·9
Millimetres of mercury ..	532	608	684	760	836	912
Pounds per square inch ..	10·21	11·7	13·1	14·6	16·1	17·5

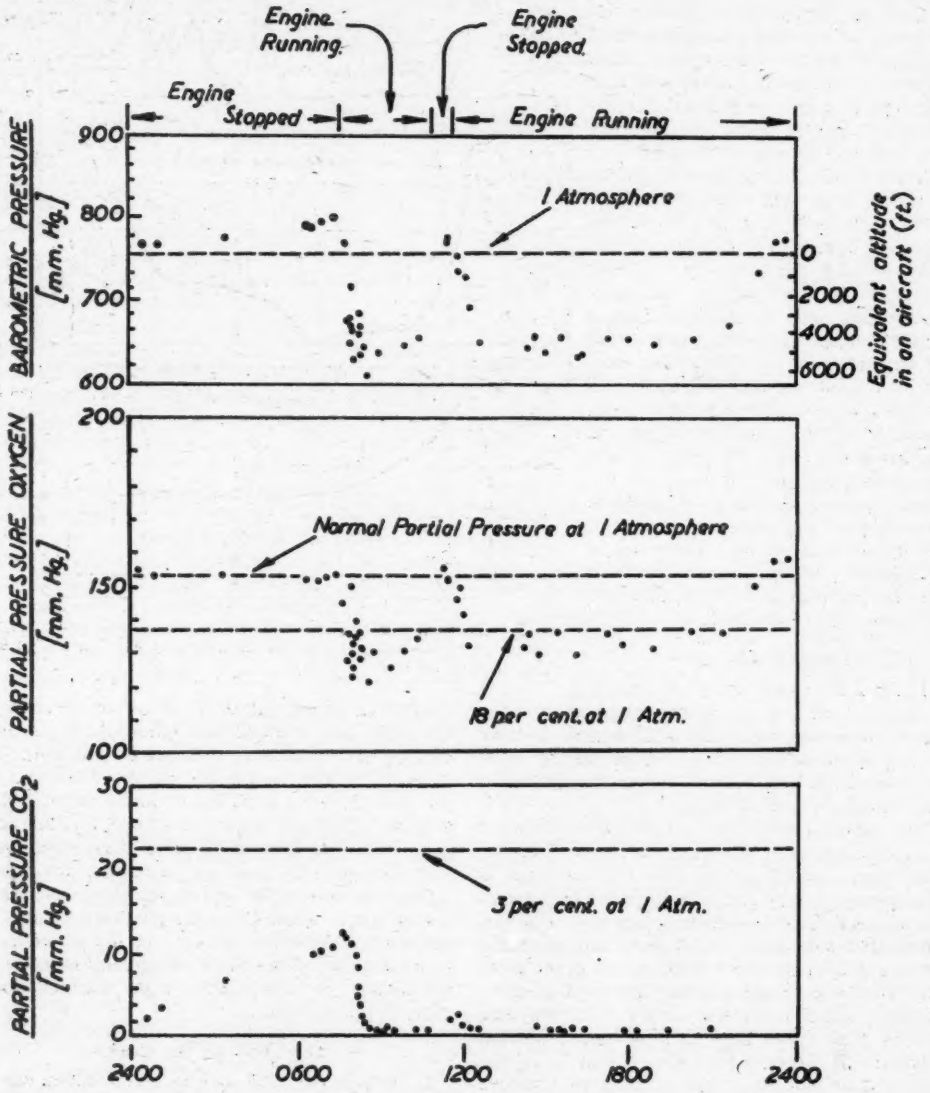

FIG. 2.—Variations in the atmospheric pressure and oxygen and carbon dioxide content on Day 20.

per cent. of one atmosphere, but the amplitude of the fluctuations is of more moderate degree.

On Day 23 (1D) in a very calm sea the effect of a sudden reduction in total engine revolutions on the pressure depression is shown clearly, and it is seen that in a calm sea pressure fluctuations are observed rarely when the crew are fully accustomed to the controls.

The pattern of the pressure variations is shown in greater detail by enlargement of the time scale in a horizontal direction in figs. 1E to 1L. The vertical scale is much the same, differing only with the calibrations of the three instruments used. Maintained reduction of the atmospheric pressure is observed to be mainly a function of the total engine revolutions, and fluctuations in pressure vary in degree in relation to the state of the sea and the length and height of the swell, the speed of the submarine, and the efficiency of the depth-keeping. Sudden severe pressure fluctuations due to errors of judgment or mechanical faults may occur occasionally, and an example of what may happen is given in fig. 3, to which reference will be made later.

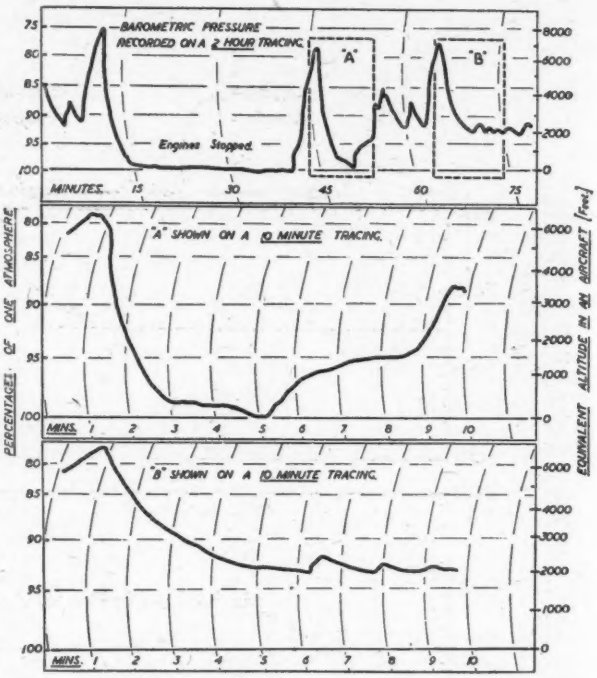

FIG. 3.—Unusually severe pressure fluctuations which gave rise to temporary discomfort in the ears or accessory nasal sinuses at the beginning of the trial.

Chemical Changes

In fig. 2 are shown the partial pressures of oxygen and carbon dioxide observed in the air of the submarine during a typical 24-hour period, submerged at a depth of 80 feet by night and proceeding at periscope depth on the main engines using the snort by day.

The partial pressure of oxygen varies with the total atmospheric pressure when the snort is in use, and when communication with the open air is discontinued it may rise with increases in pressure due to such factors as high pressure air leakages within the submarine, or it may fall gradually because of the respiratory requirements of the crew. The latter will be considerably increased if heavy physical exertion is necessary at any time. Physical activity is therefore kept to a minimum when a submarine is submerged for long periods at depths greater than snorting depth in order to conserve the supply of oxygen. The high engine revolutions when snorting on Day 20 were associated with between 20 and 25 per cent. reduction in the partial pressure of oxygen in the air within the submarine.

During the periods submerged with the snort lowered the partial pressure of carbon dioxide steadily increased until the fresh air supply through the snort was re-established (chemical absorption of CO_2 carbon dioxide was not carried out). A temporary submergence during the forenoon of this day (see also figs. 1C and G) was associated with a slight further rise of carbon dioxide, and increase of the partial pressure of oxygen to the normal level.

Periods without fresh air ventilation are rarely sufficiently prolonged under peacetime operating conditions to allow the accumulation of harmful amounts of carbon dioxide; and the periodic or continued use of the snort will greatly reduce the probability of undesirably high accumulations occurring in war time.

The Effect on the Crew

In the past the main environmental factors which required control in submerged submarines, which had no air supply from the surface, were progressive depletion of atmospheric oxygen associated with accumulation of carbon dioxide which were the direct results of the respiratory processes of their crews.

Oxygen lack, even when it is mild, is known to be associated at night with diminished visual acuity and an increase in the time required for dark adaptation ; and with more severe degrees of anoxia lowered powers of judgment and discrimination, possibly associated with confident unawareness, occur in some people. Thus in the recent war Royal Air Force pilots used oxygen continuously when flying by night, and at altitudes above 10,000 feet by day. The effects of oxygen lack are aggravated by physical exertion, or by any factor which interferes with oxygenation of the tissues such as mild carbon monoxide intoxication.

Carbon dioxide accumulation in the atmosphere will cause headaches, nausea, malaise, and fatigue in some individuals towards the end of long dives (12 to 20 hours) if the facilities for air purification are not available ; and these symptoms may be renewed or intensified, or may even occur for the first time after restoration of fresh air supplies on surfacing or on commencing to snort.

No ill effects result from the moderate increases of pressure sustained during submerged periods, provided caution is exercised at the time of opening up to fresh air.

The introduction of the snort has enabled fresh air to be supplied and carbon dioxide to be eliminated whilst submarines are still submerged. This greatly simplifies the problem of air purification under these operating conditions, but it also introduces the new problems of reduced pressures and fluctuating pressures. The effects of these may be subdivided into those due to (1) reduced pressure, (2) sustained pressure fluctuations, and (3) sudden pressure fluctuations.

Reduced Pressures.—The effects of pressure reductions such as those shown in figs. 1F to 1L are simply those of the associated degree of oxygen lack. In fig. 2 it is observed that this would correspond to breathing 16 per cent. oxygen at atmospheric pressure when snorting with high-engine revolutions (640 revs.) or even lower percentages under certain conditions described here. Thus, by night the visual efficiency of men using the periscope whilst snorting might be impaired ; and, if careful control was not ensured of the pressures to which the crew were exposed, especially in rough weather, prolonged exposure to an atmosphere poor in oxygen might increase fatigue and impair judgment and general efficiency to an unacceptable degree.

Continuous Pressure Fluctuations.—The pressure fluctuations recorded on Day 7 represent unusually severe conditions which would probably be experienced only if it was necessary to proceed with fairly high engine revolutions at slow speeds in a rough or choppy sea and if the depth-keeping was poor. These conditions did not cause a crew who had grown accustomed to the usual range of pressure changes to complain of immediate discomfort, but the accumulated effects of exposure throughout the day were thought to induce greater general fatigue than would otherwise have been experienced, and mild anoxia may well have contributed to this. About one third of the crew also complained of headaches, which were generally relieved after snorting finished for the day. It is observed that the pressures were equivalent to spending the day in an aircraft continuously ascending and descending to and from varying heights between 1,000 and 8,000 feet at intervals of a few minutes.

Sudden Pressure Fluctuations.—Pressure fluctuations such as those indicated in figs. 1E to 1L did not cause discomfort or arouse complaints from the crew. More sudden changes, however, such as are depicted in fig. 3, which resulted from temporary loss of control of the depth of the submarine at the beginning of the cruise, added to the general picture given above by inducing temporary symptoms of acute sinus or otitic barotrauma in those individuals who were unable to equalize, with the pressures in the submarine, the pressures within their accessory nasal sinuses or middle ear cavities. This was generally due to temporary blockage of the sinus foramina or eustachian tubes by such factors as mild congestion or catarrhal exudate due to chronic catarrh or acute coryza. Difficulty in clearing the eustachian tubes was generally overcome by men with temporary blockages or unaccustomed to pressure fluctuations, by swallowing, by opening the mouth and retracting the jaw, or by pinching the nose and puffing out the cheeks. Equalizing the pressures was performed automatically by the great majority of individuals after a few days snorting.

Acute dental pain was caused on one occasion when the pulp cavity of a rating's tooth was exposed by extensive caries to sudden pressure changes of fairly severe degree.

The pressure changes shown in fig 3 were experienced before the crew had grown accustomed to fluctuating pressures, and mild symptoms of sinus or otitic barotrauma were experienced by a number of men. The rise of pressure following a sudden reduction was the feature which generally caused discomfort, and with sudden fluctuations of this type it appeared that the rate of change of pressure was of greater importance than the amplitude of the change. Thus the rise of pressure graphically illustrated by tracing " A " caused ratings to complain of unpleasant symptoms, but the more gradual rise shown in tracing " B " did not.

The threshold rate of pressure change at which discomfort was experienced by certain individuals during more severe pressure fluctuations was observed to be of the order of 0·04 to 0·06 inches of mercury per second, although the great majority of healthy men were unaffected once they had become attuned to the more usual type of pressure variation. The changes of pressure related to normal starting or stopping of the engines did not cause discomfort.

In practice pressure changes causing symptoms are experienced infrequently with a trained crew and a carefully handled submarine. Before and after

this cruise the men were examined medically, and also by an ear, nose, and throat specialist who measured their hearing acuity with an audiometer, and from the detailed observations made there is no evidence that such ill effects as may be experienced amount to more than those which persons travelling in aircraft must endure at times. It is necessary to add, however, that after exposure to the unusually severe pressure fluctuations shown in fig. 3 nearly half the crew showed abnormal congestion of their ear drums. These appearances lasted only for a period of hours, or in a few cases for a few days, despite the fact that the men were exposed to pressure fluctuations of considerable, though less severe degree, for most of this time.

One further factor should be mentioned in discussing these pressure changes and the phenomena related to the use of the snort. In certain circumstances—if the engine should be stopped following sudden submergence with the engines running, or when snorting with a following wind—traces of carbon monoxide may be detected in the submarine air. Whilst the degree of this hazard as it has been observed so far would not be harmful alone, the additional anoxia which might result at times in persons already experiencing mild oxygen lack due to low atmospheric pressure would be unacceptable for a prolonged period under operational conditions. Measures for identifying and controlling carbon monoxide are therefore of practical importance.

Conclusion

The environmental factors described here were observed under trial conditions with prototype equipment, and some of the crew were unaccustomed at first to the novel operating conditions. The possible environmental stresses which might affect the efficiency of the crew have been discussed in some detail, but it is emphasized that these are all readily controllable, and the likelihood of undesirable strain being placed on members of a crew will be progressively reduced in future operations by modification of the design of the equipment and control systems, and as a result of operational experience.

In the same way as the aircraft pilot may impose stresses or discomfort on himself or his passengers by steep turns, power dives or other ærobatics, so may the mishandling of a submarine inflict unfavourable environmental conditions on the crew. In war the operational situation will demand at times that unfavourable conditions of varying degree shall be accepted, when the alternative course will involve greater hazards at the hands of the enemy, or when an important attack must be pressed home in special circumstances. The submarine captain, in assessing the tactical situation, can take full account of any unusual environmental stresses which may be imposed on his crew at these times only if he is well informed of the basic physiological facts and their practical implications, and has at his disposal accurate direct reading instruments for indicating the conditions prevailing within the submarine.

There is no evidence so far to suggest that special conditions will occur in snort-fitted submarines to influence adversely the health or efficiency of the crews, provided that the provision of an optimal environment for the men is borne in mind at all times by those responsible for designing the submarines and for handling them after they are built. On the contrary it is thought that the domestic comfort of the crews will be considerably increased by the reduced motion of the submarine when submerged, by the abolition of the wet and draughty conditions which formerly resulted when a submarine was on the surface in rough weather, and also by the concession allowed the crew of being able to smoke when submerged. It is equally certain that neglect to consider human factors adequately will result in loss of efficiency.

In the Royal Navy when submarines are designed or operations are planned the application of advances in physiology or psychology is ensured by the close co-operation of physiologists, psychologists, and submarine medical officers with the designers of submarine equipment and the operational commands.

The future development of submarines requires that knowledge shall be as complete as possible on the effect of the different environmental variations which may be encountered on judgment and discrimination, visual or auditory functions, efficiency in the performance of psychomotor tasks, or in aggravating fatigue. The effects of prolonged or repeated exposure, or of different combinations of factors, merit special attention. A fascinating field for further practical observations and for fundamental research is thus opened up, and the application of basic knowledge acquired in this way may be expected to extend beyond the particular naval requirement considered here.

This account summarizes the main physiological findings of a preliminary investigation of the effects of "snorting" carried out for the Royal Naval Personnel Research Committee of the Medical Research Council.

I am indebted for invaluable advice to the members and scientific associates of that Committee; and particularly to the Staff of the Royal Naval Physiological Laboratory for advice and assistance before the cruise, and to Mr F. E. E. Smith of the Medical Research Council's Group for Research in Industrial Physiology for preparing Illustrations 1 to 3.

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HEALTH AND ENVIRONMENTAL CONDITIONS IN BRICKWORKS

BY

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This survey is based on experience gained at three of the four brickworks of the Butterley Company Limited, in which altogether 144 persons are employed. At three of these works the "stiff plastic" process of manufacture is employed, but at the fourth the "wirecut" or "fully plastic" method is used. Since the workers employed are, at best, semi-skilled and tend frequently to change from one job to another, it is not possible to classify their occupations in an entirely satisfactory manner, but a rough list has been attempted as follows:

clay-getting
grinding and screening
brickmaking
tramming to kilns
setting
fitting and maintenance
burning
drawing
labouring (i.e., kiln cleaning and reloading from stock)

The works owned by the Company are typical of a large number of brick-producing units which together yield a high proportion of the total bricks manufactured in England. The buildings and general environment are of a kind usually met with in the industry, and for this reason it is felt that conclusions based on the results of this survey can claim to give a fair picture of a considerable section of the brickmaking industry.

The Clays and the Processes

The so-called "clays" from which bricks are made in this country are mixtures of complex compounds of alumina and silica in widely varying proportions, together with impurities in the form of free silica, iron oxide, lime, magnesia, alkalis, and a certain amount of decomposed organic matter. Of these impurities, the most important from the brickmaker's point of view is iron oxide. In the rare instances where little or none occurs the finished brick is a white or pale yellow colour. Three to 5 per cent. of iron causes a yellow to buff colour, and a higher proportion, up to 12 per cent., gives varying shades from salmon-pink to deep red. Even higher iron contents are occasionally met with, and such clays, if otherwise suitable, can be used for the manufacture of blue bricks. All the bricks produced at the works under review have an average iron content and burn to a red colour. The chemical constitution of the clay or shales from which such bricks are made is of the range given in Table 1.

TABLE 1

CHEMICAL CONSTITUTION OF CLAY OR SHALE USED FOR BRICKS AT BUTTERLEY COMPANY WORKS

	Percentage	
	Minimum	Maximum
Alumina	17·8	24·5
Total silica	43·0	60·7
Iron oxide	3·6	7·4
Calcium carbonate	Trace	
Magnesium carbonate ..	1·6	1·8
Organic matter and carbon ..	5·9	8·9
Other constituents (calcium sulphate, sodium chloride, etc.)	5·4	18·4
Moisture content	1·4	2·4
"Free silica"*	12·4	29·1

* By chemical analysis.

In three cases, the supply of material comes from a "clay hole" or quarry, adjoining the brickworks, but in the fourth it takes the form of shale from a nearby colliery.

Stiff Plastic Brickmaking.—In the case of bricks made by the stiff plastic process, the shale or clay is brought down from the quarry face by excavators and loaded directly into wagons which are trans-

* Now Divisional Chief Scientist, National Coal Board, East Midlands Division.

ported to the works by an endless chain or rope haulage system. It is then reduced to a fine powder in grinding pans. These pans have perforated bottoms, and as they revolve the material is crushed under heavy rollers; when fine enough it passes through the perforations into a pit, from which it is collected by a bucket elevator and delivered to the screening chamber. This is situated on the top floor of the building. In this chamber the ground material passes over sieves formed by a series of parallel wires, which take out the particles too coarse for brickmaking. Such particles gravitate back to the grinding pans. The material which passes through the sieves falls on to a stock-heap from which the brick machines are fed through holes in the floor. The brickmaking machine consists of a mixer, where sufficient water is added to form a stiff paste, and a pugmill or compression machine, which fills a series of moulds. The "clots" thus formed, are then automatically pressed into bricks. All machines of the stiff plastic type demand copious lubrication, both of the moulds and of the press dies, to prevent the adhesion of the clay paste to the metal. A continuous spray of oil is used for this purpose. The bricks are taken off the machine by hand and loaded on to trolleys. Having a moisture content of only about 18 per cent., they are stiff enough to be set directly into the kiln.

Wirecut or Plastic Brickmaking.—Here again the material is taken from the clay face by mechanical excavator and transported to the works by endless-chain haulage. The wagons are emptied into a feeder, from which the clay passes into a wet pan where water is added and the whole is milled into a plastic mass. The clay is squeezed through a series of slots in the bottom of the pan, after which it passes through several pairs of finely set crushing rollers and is delivered into a pugmill. From this machine it is extruded in a continuous column of very plastic clay, the cross-section of which is that of a green brick. This column is divided into three-foot lengths, which are then passed on to a removable pallet at right angles through a frame supporting parallel wires which cut the column into nine or ten bricks. The pallets are then loaded on to trolleys designed to carry about sixty bricks. Wirecut bricks at this stage of manufacture are too soft to permit being set directly into the kilns and they therefore spend a period of two or three days either on a heated drying floor or in some form of drying chamber, after which they are transported to the kiln.

TABLE 2

SHOWING THE COOLING POWER AS ASSESSED BY MEANS OF THE KATA THERMOMETER AND THE AIR TEMPERATURE IN DEGREES FAHRENHEIT FOR WET AND DRY BULBS (THE AIR VELOCITY IN FEET PER MINUTE IS ALSO OBTAINED FROM THESE READINGS)

Process	Date of reading	Hour of reading	Temperature assessed by whirling psychrometer		Relative humidity	Cooling power assessed by Kata thermometer		Air velocity in ft. per minute
			Dry-bulb	Wet-bulb		Dry-bulb	Wet-bulb	
Brick setting (chamber empty) ..	April 3	12.00	73	—	—	9·00	—	250
Brick setting (chamber quarter full)	April 4	10.00	78	63	42%	6·25	—	—
Cleaning out	April 3	10.30	98	72	27%	1·00	11·5	10
Brick drawing (chamber nearly empty)	April 4	10.30	75	63	51%	6·00	—	70
Brick drawing (chamber nearly full)	April 3	11.15	75	68	70%	5·25	—	50
Space against chamber tapped same morning*	April 3	12.30	95	72	58%	2·00	—	450
Cleaning flue hole in empty chamber	April 4	12.30	89	68	35%	2·50	25·0	190
Kiln No. 1: Above chambers Hot end	April 4	11.00	94	68	25%	5·50	15·0	320
Cool end	April 4	11.30	83	63	31%	5·00	12·5	220

* This space was too hot to allow readings to be taken on arrival, but the figures given here were obtained some two hours later, that is, some five or six hours after tapping.

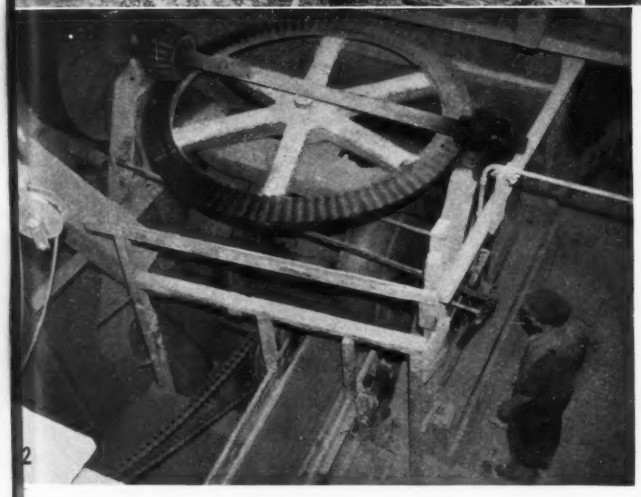

FIG. 1.—The excavator deposits clay into a wagon, which is moved by rope haulage up an inclined plane where the clay is transferred to a conveyor belt which carries it to the brickworks.

FIG. 2.—A view from above, showing the heavy rollers and grinding pans which reduce the clay to a fine powder.

FIG. 3.—The fine dust is raised by elevators from the grinding pans to the screens, one of which is seen in this picture. The workman is directing the flow of ground clay into the aperture through which it passes to the presses on the floor below.

Firing.—Brick kilns nowadays are generally of the continuous type which are constructed in a series of sixteen to twenty or more, so as to form a continuous tunnel. These kilns or chambers are set with bricks from floor to roof at the rate of about six to eight chambers per week. The bricks remain stationary in the kiln, but a body of fire circulates through the whole eighteen kilns in about three weeks.

During this time a chamber of bricks, after being set and the entrance to the kiln bricked up, undergoes a period of approximately three days' drying, six or seven days' pre-heating, three days during which actual firing takes place, followed by five to six days' cooling, after which the bricks are drawn and the chamber is cleaned out ready for refilling. The firing is done from the roof of the kilns, which are provided with small openings known as firing holes, to enable the coal to be introduced from above. Combustion takes place among the bricks.

Environmental Studies

Atmospheric Conditions.—The environmental studies were carried out at a stiff plastic brickworks.

FIG. 4.—The process of taking the bricks off the press is done by hand. Note the careful guarding of a dangerous machine. Taking off the bricks brings the hands of those engaged on this work into contact with oil.

FIG. 5.—The bricks are stacked on a trolley and are then taken to the kiln.

FIG. 6.—The trolley is pushed by hand to the kiln along a covered way which, however, is open to the weather on one side.

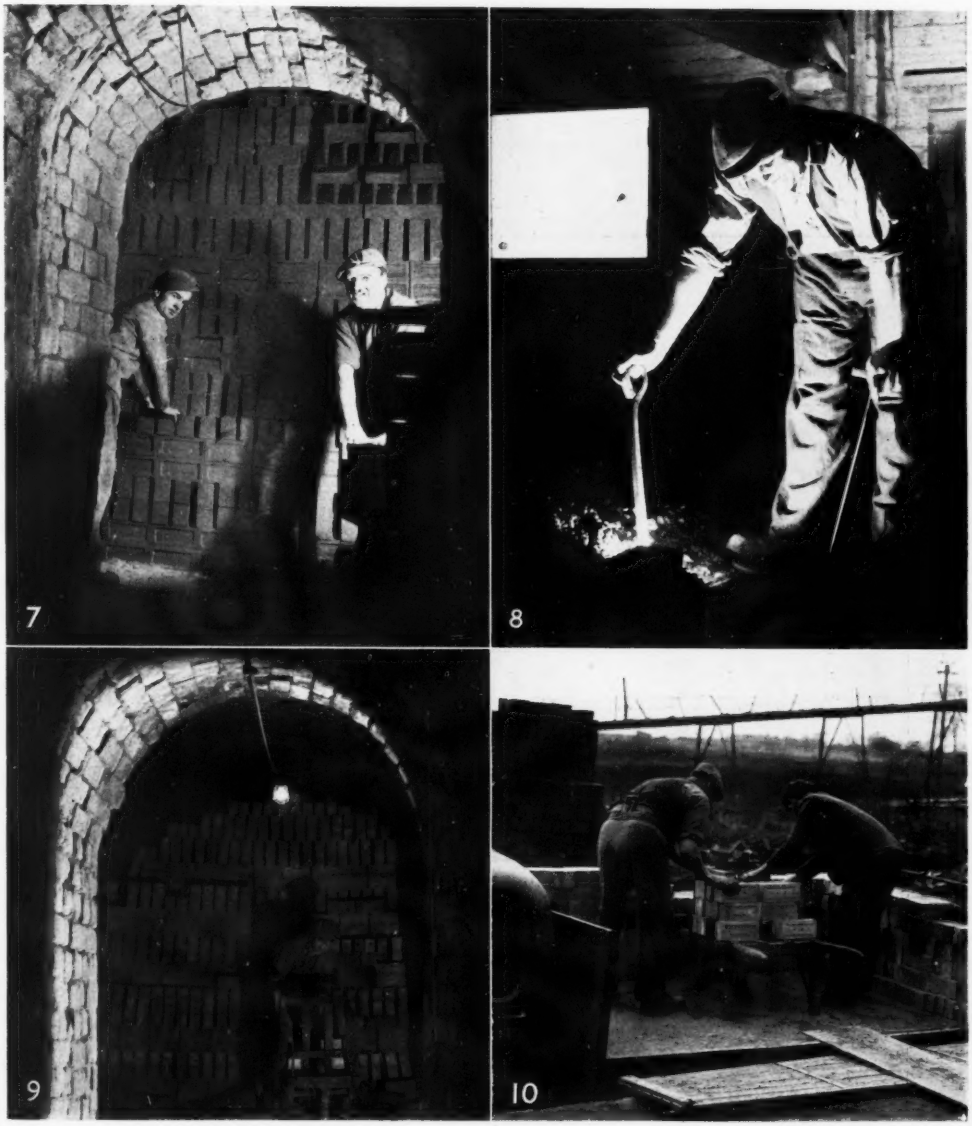

FIG. 7.—The green bricks are stacked by hand from floor to roof of the kiln.

FIG. 8.—Firing is done from above the kilns. The brick-burner is a highly-skilled person.

FIG. 9.—The bricks, having been fired and allowed to cool, are drawn off by hand.

FIG. 10.—The barrows are wheeled direct onto the waiting lorries, where the bricks are again stacked by hand. In the background can be seen the inclined plane by which the wagons reach the brickworks.

Table 2, shows the results obtained with the Kata thermometer and the sling psychrometer. The temperature readings are high, ranging from 73° F. to 78° F., but such a state of affairs is inherent in the nature of the processes. As might be expected, the cooling power is rather low; in the case of brick-drawing the relative humidity is high when the chamber is full.

Dust Hazards.—The estimation of the dust risk was determined according to a technique similar to that previously described by us (Keatinge and Potter, 1945) and amplified subsequently in greater detail by one of us (Potter, 1946).

The Mass Concentration of Air-borne Dust.—Twenty determinations of the dust hazard were under-

TABLE 3
SUMMARIZED OBSERVATIONS

Sample No.	Operation and location	Mass concentration (g. per 1,000 cu. ft.)		No. of particles per c.cm. 5·5 microns 0·9 microns	Sulphur-dioxide, parts per hundred million of air
		Below 5·5 microns (1)	Whole dust (2)	(3)	(4)
	Kilns :				
10	Brick-drawing kiln 1 : chambers 8, 9, and 10	—	1·2	—	—
2	Brick-drawing kiln 2 : chamber 11	—	0·5*	—	28
13	Brick-drawing kiln 1 : chamber 11 (windy)	—	4·6	—	17
18	Brick-drawing kiln 1 : chamber 4 (very windy)	0·12	4·9	326	—
1	Brick-drawing and cleaning-out kiln 1 : chambers 8, 9, and 10	—	7·2	—	—
19	Cleaning-out kiln 1 : chamber 3	0·12	2·7	340	—
24	Chamber ready for cleaning out, open three days	—	—	—	76
25	Firing floor above kiln 2	—	—	—	41
8	Stacking green bricks kiln 2 : chamber 2	—	0·1	—	40
14	Stacking green bricks kiln 2 : chamber 3	—	0·3	—	—
20	Stacking green bricks kiln 2 : chamber 4	0·008	—	17	—
	Dust Mills :				
6, 17	General body on ground floor near presses	0·008	0·2	31	—
7	Top floor, outer room to screen B	—	0·9	—	—
15	Top floor, outer room to screen B	0·06	2·0	169	—
3	Top floor, screen B	—	4·6	—	—
21	Top floor, screen B	0·16	3·5	601	—
11	Top floor, screen B	—	3·7	—	—
4	Top floor, screen A	—	4·6	—	—
16	Top floor, screen A	0·15	4·8	455	—
22	Top floor, screen A	0·08	4·2	257	—
5, 12	Top floor, screen A	—	1·2	—	—
23	Top floor, screen A	0·02	1·4†	105	—

* This sample was a continuous one. Normally samples were discontinued when the kiln was not occupied.
† This sample represented a place where the worker stood out of the dust when not needed at the screen.

taken. These were carried out when workers were in the environment, each sample being taken by means of a hand pump attached to a filter. Eight of these were taken actually in the kilns, and the remaining twelve in the environment of the dust screen which feeds the crushed shale to the mixer. These were considered to be the dustiest occupations.

The cycle of operations in the kilns is (1) loading the green bricks; (2) unloading the fired bricks out of the kiln; (3) cleaning out the coke and ashes from the kiln. Operations 2 and 3 may occur simultaneously.

At these times the highest mass concentration of dust was observed. The maximum concentration was 7·2 g. per 1,000 cu. ft.

The mass concentration of dust during emptying the kilns depends on outside conditions and whether the bricks are being removed from the mouth of the kiln or from the interior. The range was from 1·2 to 4·9 g. per 1,000 cu. ft. The dust is lodged on the tops of the bricks and is largely the ash from the coal which is fired from the top. When the brick is removed the ash is dislodged, and in windy weather the dust can cause physical discomfort.

There is very little dust associated with the stacking of the kilns with green bricks. An average concentration amounted to only 0·2 g. per 1,000 cu. ft.

To deal with the ground shale there are two screens in separate rooms each serving different moulding machines. In each room a worker is maintained to keep the feed constant. Here again, conditions are variable depending on the position of the operator, ventilation, and the dryness of the powder. Both rooms are very dusty. In one room a belt carries part of the dust to an outer room where it is delivered again to a hole in the floor. Owing to the open nature of this room and the small feed, the dust concentration affecting the operator is much lower than is the case for the other two workers.

The mass concentration near screen (A) varied from 1·2 to 4·8 g. per 1,000 cu. ft., an average value being 3·2. The operator will tend to be in the lower concentration when he is standing away from the screen.

Near screen (B) the concentration varied from 3·5 to 4·6 g. per 1,000 cu. ft. and the average is 3·9.

In the outer room adjoining screen (B) the concentration is not greater than 2 g. per 1,000 cu. ft. with a mean value of 1·4 g.

Downstairs below the screens where the shale is being ground and the presses are working the average dust concentration is only 0·2 g.

Numerical Concentration of Dust Particles.—Nine of the above samples were selected as generally representative, and the air borne dust was examined in order to assess the number of particles present in each cubic centimetre of air of a size which may be regarded as a potential hazard to health. Dust particles larger then 5·5 microns have been ignored

TABLE 4

PARTICLE FREQUENCY DISTRIBUTION OF AIR BORNE DUSTS*

Description	Drawing bricks (very windy)	Cleaning out a chamber	Setting green bricks	Dust screen A	Dust screen A	Dust screen A, out of main dust	Dust screen B	Outer room to screen B	General body, ground floor
Sample number	18	19	20	16	22	23	21	15	17
5·5 microns	19	15	1	23	15	4	24	8	1
4·4 microns	25	24	2	24	11	2	16	12	2
3·5 microns	23	31	1	36	13	4	37	14	1
2·6 microns	40	52	4	52	28	15	85	22	3
1·8 microns	56	82	6	122	72	27	160	46	7
0·9 microns	163	136	3	198	118	53	279	67	17
Total (5·5 to 0·9)	326	340	17	455	257	105	601	169	31
Grammes per 1,000 cu. ft. calculated	0·12	0·12	0·008	0·15	0·081	0·024	0·156	0·060	0·008
Weight % of total dust ..	2·4	4·4	4	3·1	5·8	1·7	4·5	3	4

* The mass concentration of the —5·5 micron dust is calculated from the specific gravity and the volume constant.

as have those smaller than 0·9 microns. (Normally the count would have been to include particles down to 0·5 microns, but the refractive index of the shale particles made examination in oil very unreliable.) A full count down to 0·5 microns would probably double the numbers given below, which are, of course, comparable with one another.

The highest number of particles was near to screen (B) when 600 particles per c.cm. were recorded. In the room adjoining screen (B) the concentrations were much lower with 169 particles per c.cm. In the vicinity of screen (A) the lowest particle number recorded was 105 and the highest 455, corresponding to the observed changes in mass concentration.

In the kilns the highest number was obtained during cleaning out, namely 340 particles per c.cm. Unloading kilns showed a high count, with 326 particles per c.cm., but the number was probably increased by windy conditions.

During the loading of a chamber with green bricks the number dropped to 17 particles per c.cm. This is comparable with conditions in the general body of the dust mill near the presses, where the number of particles per c.cm. was 31.

Extent of Risk.—Although some of the dust concentrations are high, the chemical constitution of the dust is such that the danger from the inhalation of free silica in these brickworks cannot be great. Nevertheless the practice of water suppression as in use at one of the brickworks could well be extended, although it may be recalled that alumina has been shown to inhibit the fibrosis-forming properties of free silica on the lung (Gardner and others, 1944). The process of manufacture of wire-cut bricks limits the risk of inhalation of dust to work in the kilns, where the hazard is comparable with that encountered in the firing of stiff plastic bricks.

Fumes.—During the cooling and cleaning of the chambers there appeared to be a considerable amount of fume present. This was tested for sulphur dioxide, hydrogen sulphide, and carbon monoxide, traces being found of the two first mentioned.

Sulphur Dioxide Concentrations.—Six measurements of the concentration of sulphur dioxide were made, five in the chambers and a sixth on top of the kilns where the coal was being fired. A seventh test was carried out in the outside air. The measurements were all made after a week-end and in clear windy weather so that our recorded concentrations are probably somewhat lower than normal. Qualitative tests were made with the starch-iodate-iodine stain (Department of Scientific and Industrial Research, 1943) and quantitative measurement by means of the volumetric method, that is to say absorption of a known volume of air in dilute hydrogen peroxide solution, the sulphuric acid thus formed being titrated with $\frac{N}{250}$ alkali. The concentrations are all expressed in parts per 100 million.

Above the kiln the concentration was 41. Coal is fed at intervals through the small opening by means of a hand shovel, the whole top floor is very open and only one man is employed at each shift. It was noticed that fumes were emitted from the top of the lids after firing.

A chamber which was ready for cleaning out, having been open for three days, gave the highest concentration—of 76. This was on the windward side. Two chambers being unloaded, one on either side of the kiln, gave concentrations of 28 and 17 respectively. In a chamber that was being loaded with green bricks the concentration was rather high at 40.

The normal air external to the brickworks was exceptionally free from sulphur dioxide, and certainly did not exceed 5. This is very low indeed, and indicates that mixing conditions in the atmosphere were very good.

Carbon Monoxide Concentration.—The palladium chloride reaction was the method used for the estimation of carbon monoxide. (Department of Scientific and Industrial Research, 1943.)

Tests were carried out above the kilns (from where the stoking is done) and in the chambers during cleaning out. No reactions whatever were noted for concentrations of 1 in 12,000 or less. Concentrations of 1 in 10,000 or less are regarded as harmless for practical purposes.

Hydrogen Sulphide Concentrations.—The Lead-acetate test was used for the estimation of this gas (Department of Scientific and Industrial Research, 1943).

Tests were carried out above the kilns, at the entrance to a chamber just tapped, and in a chamber during cleaning out. All three positions gave positive results, but the concentrations were very low, namely considerably less than one part per 1,000,000 in the first two positions and less than one part per 500,000 in the chamber during cleaning out.

Mineral Oil.—Although it has not been possible to find out the country of origin of the oil, it has a specific gravity of 849 and its refractivity is within the range of 5,540 to 5,500, so that on the basis of these findings its carcinogenic properties should not be high (Twort and Lyth, 1933).

Health Studies

A study of the occupational mortality figures in the Registrar General's Decennial Supplement (1931) relating to "makers of bricks, unglazed tiles, kiln and oven men not making earthenware, china or terra cotta," although apt to be misleading in some respects, nevertheless shows the low ratio of eighty-seven in each of the above groups expressed as a standardized mortality rate.

One hundred and forty-four men are employed, and of these one hundred have been submitted to medical examination, while radiography of the chest was carried out in seventy-three cases. Two of the brickworks have recently been re-opened and all those starting work in them—thirty-seven persons—have been examined. The remaining sixty-three have all been employed at a larger brickworks and were examined on a routine survey, which included all save three of the workers.

The average length of employment in the brickworks industry was 7·88 years per worker. The results of the investigation are given in Tables 5, 6, and 7, and it will be noted that the physical condition of those examined was on the whole satisfactory. These findings therefore afford confirmatory evidence of the good standard of health of the brickworkers; nevertheless it must be borne in mind that the vast majority examined were young men whose physical condition might be expected to be good. The radiographic appearances of the lungs were singularly free from changes due to dust, although in only two cases had there been a dust hazard of any magnitude. These were both young men, aged 25 and 22, who had been working in the dust mill for a considerable time; but even in them the changes due to dust were minimal.

TABLE 5

SHOWING PHYSICAL DEFECTS FOUND IN ONE HUNDRED PERSONS EXAMINED AT FOUR BRICKWORKS OF THE BUTTERLEY COMPANY LIMITED

Physical defects found	Number of persons in each age group (years) showing such defects			
	14–25	26–35	36–45	Over 46
No physical defect noted	10	11	3	1
Respiratory conditions	1	3	1	2
Enlarged tonsils ..	9	—	—	—
Dental conditions ..	6	4	4	2
Reduced vision ..	2	4	2	7
Low mental grade ..	1	1	—	1
Defects of cardio-vascular system	—	1	5	—
Defects of central nervous system	3	1	1	1
Hernia and weakness in inguinal rings	2	2	1	2
Skin	7	4	1	1
Miscellaneous ..	7	6	12	1
Total	48	37	30	18

TABLE 6

SHOWING LUNG CHANGES IN SEVENTY-THREE MEN X-RAYED AT FOUR BRICKWORKS OF THE BUTTERLEY COMPANY LIMITED

Age group (years)	Class				
	I	II	III	IV	V
14–25	16	10	—	—	—
26–35	5	24	1	—	—
36–45	1	10	—	—	—
46 and over ..	—	5	—	—	1

Class I, normal lung;
Class II, increased markings but not beyond normal limits for a town dweller;
Class III, early reticulation;
Class IV, first-stage silicosis;
Class V, second-stage silicosis.

One new entrant to the brick-making industry, a man aged 49, showed radiographic appearances indistinguishable from classical silicosis. He had previously been a bricklayer's labourer, and the changes seen in the lung therefore remain unexplained, although we have from time to time observed early dust changes in the lungs of bricklayers and their labourers.

Two cases showing keratotic changes in the skin were seen in men aged 46 and 36, who had been exposed to mineral oil for a long time; biopsy, however, showed no evidence of malignant changes. The occurrence of skin effects following the use of mineral oil in brickworkers has been noted previously (Henry, 1946) but needs to be stressed.

Only one compensatable accident took place during the twelve months in which this survey was being conducted. This was a case of amputation of the terminal portions of the distal phalanges of the third and fourth fingers of the right hand in a boy aged fifteen years who was operating a brick press.

Discussion

The possible hazards of brickworkers are: (1) dermatitis and keratotic changes in the skin associated with the use of mineral oil; (2) the inhalation of dust in those working in the mills;

TABLE 7

OCCUPATIONAL HISTORY AND PHYSICAL DEFECTS FOUND ON EXAMINATION OF WORKERS EMPLOYED AT FOUR BRICKWORKS OF THE BUTTERLEY COMPANY LIMITED

No.	Age	Period in brick-works	Present occupation and how long	Principal occupation while employed in brickworks	Previous employment and how long	Defects	*X*-ray class
1	14	6 mth.	On the press 6 mth.	On the press	None	Cannot read	..
2	14	Few weeks	Taking off, few weeks	Taking off	None	None	I
3	14	3 mth.	Tramming, 3 mth.	Tramming	None	None	I
4	14	3 mth.	Tramming, 3 mth.	Tramming	Cinema operator, 6 mth.	Oral hygiene poor	II
5	14	3 mth.	Labourer, 3 mth.	Labourer	None	Oral hygiene poor	I
6	14	2 mth.	Labourer, 2 mth.	Labourer	None	None	I+
7	15	2 mth.	Labourer, 2 mth.	Labourer	Farm labourer, 12 mth.	Ununited fracture left ulna styloid; tonsils plus; dry skin; carious teeth	I
8	15	3 mth.	Labouring	Labouring	None	None	I
9	15	1 yr.	Taking off, 12 mth.	Taking off	None	Carious teeth	I
10	15	1 yr.	Labourer, 12 mth.	Labourer	None	None	I
11	15	1 yr.	Taking off, 12 mth.	Taking off	None	None	II
12	15	1 mth.	Cleaning up	Cleaning up	Blacking fireplaces, 6 mth. Making boxes, 10 mth.	Operation for hernia at 5 yr.	I
13	15	4 mth.	On the press	On the press	None	Tonsils plus	I
14	15	1 mth.	Wheeling	Wheeling	Trimming in a shoe factory, 2 yr.; cutting at crisp factory, 1 mth.	..	..
15	15	10 mth.	Brickmaking, 10 mth.	Brickmaking	Iron works, constructional dept., riveter, 5 mth., drawing off, 13 mth.	Carious teeth; tonsils plus	I
16	16	3 mth.	Mixing and dust room, 3 mth.	Mixing and dust room	At home 12 mth.; colliery 12 mth.; farm labourer 3 mth.	Vision R. 6/36, L. 6/24, B. 6/36; oral hygiene poor	..
17	16	2 yr.	Labourer, 24 mth.	Labourer	None	Gums infected with carious teeth	..
18	16	3 mth.	Labourer, 3 mth.	Labourer	Cinema operator, 24 mth.	Teeth carious; bilateral pes cavus	II
19	17	1 mth.	Dust room, 1 mth.	Dust room	Laundry boy 12 mth.; woodyard 24 mth.	Acne of face	..
20	17	6 mth.	Taking off, 6 mth.	Taking off	Dye worker 3 yr.	Tonsils plus; left varicocele	I
21	17	8 mth.	Taking off, 8 mth.	Taking off	Foundry 3 yr.	..	II
22	17	6 mth.	Labourer, 6 mth.	Labourer	Foundry labourer 2 yr.; market gardens; labourer 1 yr.	Nil	I
23	17	2 yr. 6 mth.	Tramming, 3 mth.	Mixing	Hair cutting assistant 6 mth.	Tonsils plus	II
24	18	2 yr. 3 mth.	..	..	Box-making 18 mth.; building 6 mth.	Dry skin	..
25	18	4 yr.	Tramming, 48 mth.	Tramming	Nil	Dry skin; some weakness of inguinal rings; suffers from frequent colds; tonsils plus; vision; near 7+ 1. 1., distant 6/24. 6/6. 6/5.	I
26	20	5 yr.	Tramming, 2 yr.	Taking off	Core-making in foundry 1 yr.	Dry skin; knee-jerks plus	..
27	21	4 yr. 3 mth.	Labouring, 54 mth.	Labourer	Shop assistant 6 mth.; Army 4 yr.	Tonsils plus	II
28	22	8 yr.	Tramming, 96 mth.	Tramming	Nil	Left tonsil plus	I
29	22	1 mth.	Labouring, 1 mth.	..	Messenger boy 1 yr.; shipyard labouring 2 yr.; rope works labouring 1 yr.; engineering labouring; G.P.O. laying cables; timber merchant labouring 1 yr.; Navy, home service and North Atlantic 3 yr.	Nil	..
30	22	4 yr. 3 mth.	Labourer, 1 mth.	Labouring and drawing	Foundry labourer, few weeks; Army, England and Singapore 2½ yr.	Dry skin	II
31	23	3 mth.	Labouring, 3 mth.	Labouring	Colliery haulage and coal face 7 yr.; sawing trees, 3 mth.	Tonsils plus; emotionally unstable	..
32	23	4 yr. 6 mth.	Fitter's mate, 54 mth.	Fitter's mate	Foundry core-maker 6 mth.; Army 4 yr.	Nil	I
33	24	6 yr.	Machine attendant	Machine attendant	Fettler in foundry 6 mth.; Army 4 yr.	Nil	II

(*Continued on next page*)

TABLE 7—(*continued*)

No.	Age	Period in brick-works	Present occupation and how long	Principal occupation while employed in brickworks	Previous employment and how long	Defects	*X*-ray class
34	24	3 mth.	Labourer, 3 mth.	Labourer	Colliery haulage 2 yr.; boot and shoe repair 2½ yr.; building trade 1 yr.; Army, N. Africa, Sicily, Italy, Austria, Home Service 4 yr.; aircraft dump 6 mth.; unemployed 6 mth.	States that he suffers from "shell shock"	..
35	24	1 yr.	Setting a week or two	..	Boot and shoe factory 2 yr.; Army, Home Service, N. Africa, Sicily, Italy, 4 yr.; packing 1 yr. 8 mth.	Operation for "brain tumour." Gets occasional blackouts when cycling	..
36	25	5 yr.	Foreman	..	Engineering works 12 mth.; Army, Home Service, Germany, France, Belgium, and Holland 5 yr.	Epidermophytosis	..
37	25	3 yr. (approx.)	Labourer	..	Pottery 1 yr.; engineering 1 yr.; farm 2 yr.; Army, France, and Home Service, 4 yr.	Appendicectomy	II
38	25	6 yr.	In dust room	Taking off, wheeling	Lorry driver's mate 2 yr.; Army, N. Africa, Sicily, Italy, and Egypt, 4 yr.	Amputation of left leg few inches below the knee. Near vision, R.J. 7, L.J. 7, B.J. 7	II
39	25	5 yr.	General work now	..	Colliery 6 weeks; Navy, foreign service, round the world, and home waters, 5 yr.	Dry skin; psoriasis left leg	..
40	26	1 mth.	General work 1 mth.	General work	Engineering apprentice 11 yr.; estate work 1 yr.	Infected gums	II
41	26	5 mth.	Clay hole; tramming	Clay hole; tramming	Fruit seller 6 mth.; colliery haulage 9½ yr.; driver's mate coal lorries 9 mth.	Mitral stenosis well compensated	II
42	27	5 mth.	Brick setter	Brick setter	Farm labourer 2½ yr.; ironworks raming up on pipes and on the conveyor 2½ yr.; Army, France, Germany, Holland, Belgium, Italy, Egypt, and S. Africa, 5½ yr.	Scabies	I+ Tenting right dome of diaphragm
43	27	2 weeks	Clay pit	Clay pit	Concrete works 6½ yr.; Army, Home Service, Burma, 6 yr.; county council road works ½ yr.	Meniscotomy right knee	..
44	27	1 mth.	Clay pit	Clay pit	Shoe trade 3 yr.; Navy, Mediterranean and Home waters 9 yr.; building trade 1½ yr.	Nil	II
45	27	6 yr.	Labourer 6 yr.	Labourer	Army 7 yr.	Left varicocele	II
46	27	6 yr.	Haulage 6 yr.	Haulage	Army 7 yr.	Nil	II
47	28	1 yr. 3 mth.	Labourer one week	Moulding	Forestry 6½ yr.; Army, N. Africa and Italy, 6¼ yr.	Malaria B.T. and B.W.	I. Calcified glands, hilar region
48	28	1 mth.	Drawing	Drawing	Farm work 6 yr.; Army, United Kingdom, Europe, 7 yr.	Nil	II
49	29	8 yr.	Slag wheeling	Slag wheeling	Army, Egypt, Italy, and Austria, 6 yr.	..	I+
50	29	11 yr.	Machine hand, 11 yr.	Machine hand	Army 4 yr.	Nil	II
51	30	9 yr.	Navvy driving, 2 yr.	Loading and shot firing	Rolls Royce; milling machine, 4 yr.	Nil	II. Ill-defined shadow right upper zone, calcified glands right lower zone
52	30	13 yr.	Brick burning, 9 yr.	Brick burning	Army 3 yr.	Nil	II
53	31	4 yr.	Labourer, 4 yr.	Labourer	Navy 13 yr.	..	II
54	31	11 yr.	Labourer, 11 yr.	Labourer	Army 6 yr.	Occasional rhonchi both lungs	II
55	31	6 mth.	Labourer, ½ yr.	Labourer	Colliery ganging 6 yr.; Army 11 yr. (P.O.W. 3½ yr. Burma)	Retro-bulbar neuritis, vision, N.L. None, R. and B.7; distant, L. None, R. 6/18, B. 6/18	II
56	32	12 yr.	Setting, 6 yr.	Labourer	Army 6 yr.	Right varicocele	II
57	32	14 yr.	Taking off, 6 yr.	Drawing	Army 4 yr.	Near vision J. 5, J. 5, J. 4; distant vision, 6/12, 6/12, 6/12	II
58	32	12 yr.	Brick burning, 10 yr.	Brick burning	Army 6 yr.	Right inguinal hernia controlled by a truss	II
59	33	8 yr.	Setter, 6 weeks	Brick wheeler	Army, S. Africa, N. Africa, Italy, and Austria, 7 yr.	Cannot read; right chronic otitis media; dysentery at 28 and a few tropical sores	II. Calcified glands hilar region, in right lower zone

(*Continued on next page*)

TABLE 7—(*continued*)

No.	Age	Period in brick-works	Present occupation and how long	Principal occupation while employed in brickworks	Previous employment and how long	Defects	*X*-ray class
60	33	4 mth.	Stoker	Stoker	Colliery haulage and coal face 5 yr.; Army, India, N. Ireland, and Home Service 13 yr.; lorry driver ½ yr.; Air Ministry constabulary 3 mth.	All teeth carious	Occasional rhonchi
61	33	2 mth.	Packing, 2 mth.	Packing	Colliery (roads 7 yr., coal face 1 yr.); Army 9 yr.	Nil	II
62	33	19 yr.	Brick burning, 8 yr.	Labouring	Nil	Chronic bronchitis and asthma; pruritus ani	II
63	33	2 mth.	Labourer, 2 mth.	Labourer	Gardening 2 yr.; porter in shop 5 yr.; celanese-spinner ½ yr.; colliery banksman 5½ yr.; Army 6 yr.	Near vision J. 7, J. 1, J. 1; distant vision 6/24, 6/5, 6/5	II
64	33	8 yr.	Labourer, 8 yr.	Tramming	Celanese, winder 1 yr.	..	II
65	34	8 yr.	Labourer in clay hole, 8 yr.	Labourer in clay hole	Colliery surface 1 yr.; woodyard labourer 2½ yr.; bus conductor 2 yr.; unemployed 7 yr.	Weak inguinal rings	I
66	35	2 mth.	Labourer, 2 mth.	Labourer	Rivet heater 1½ yr.; chemical works 8½ yr.; Army 11 yr.	Nil	II
67	35	19 yr.	Kiln work, 2 yr.	Labourer	Farm labourer 1 yr.; railway winding 1½ yr.; colliery labourer 2 yr.	Carious teeth; distant vision left eye 6/18	I
68	35	2 mth.	Labourer, 2 mth.	Labourer	Rivet heater 1½ yr.; chemical works 8½ yr.; Army 11 yr.	Nil	II
69	35	22 yr.	Grinding pans, 3 yr.	Stock chamber, 16 yr.	Nil	Traumatic amputation of right forearm; carious teeth	III
70	35	18 yr.	Taking off, 18 yr.	Taking off	Army 3 yr.	Nil	II
71	35	18 yr.	Drawing, 17 yr.	Drawing	Army 3 yr.	Nil	II+
72	36	22 yr.	Fitter, 15 yr.	Fitter	Nil	Varicose veins; keratosis right leg	I. Numerous calcified glands both hilar region
73	36	21 yr.	Setter, 18 yr.	Setter	Shop assistant 1 yr.; colliery, knocking clips off, 1 yr.	Carious teeth; distant vision R. 6/12, L. 6/9, B. 6/6	..
74	36	21 yr.	Brick burning, 21 yr.	Brick burning	Colour works 1 yr.	Nil	II
75	36	20 yr.	Clay hole, 18 yr.	Clay hole	Nil	Deaf and dumb; enlarged cervical glands	II
76	36	5 mth.	Labourer, 5 mth.	Labourer	Farm labourer 4 yr.; oil fields labourer 2½ yr.; railway porter 2 yr.; odd jobs 4 yr.; butcher ½ yr.; threshing 1 yr.; Army	Cataract right eye; very highly arched palate; varicose veins left leg	II
77	37	9 yr. 8 mth.	..	In the mill	Biscuit factory 1 yr.; electrician's labourer ½ yr.; Army, India, Palestine, Egypt 9⅝ yr.; abrasive machines ⅝ yr.	Manipulation of feet in Army	..
78	39	25 yr.	Foreman	Wheeling and setting	Nil	Fractured right arm; movement of elbow limited; pleurodynia each year, 1937–1942	..
79	40	26 yr.	Labouring	..	Forge	Operation for right inguinal hernia at 36 yr.	..
80	40	1 mth.	Burner	Burner	Cowman ½ yr.	Carious teeth	..
81	41	23 yr.	Bricklayer and plasterer 2 yr.	Brick setting 11 yr.	Farm labourer 4 yr.	Nil	II
82	41	6 yr.	Labourer, 6 yr.	Labourer	Colliery surface 12 yr.; celanese 4 yr.; painter 1 yr.	Blood pressure 167/102; ? old tuberculous hip, leg shortened by approx. 6 in.; no bruits but slight enlargement	II
83	41	22 yr.	Labourer in clay hole, 18 yr.	Labourer	Carter 2 yr.; farm labourer ½ yr.; engineering 1½ yr.	Bilateral pes cavus	II
84	43	24 yr.	Brick burning, 11 yr.	Clay pit, 12 yr.	At home 2 yr.; gardening 3 yr.	Nil	II+
85	43	28 yr.	Brick burning, 28 yr.	Brick burning	Army 1 yr.	Enlarged heart; blood pressure 168/118	II
86	43	6 yr.	Labouring	Watchman	Colliery underground 21 yr.; unemployed 2 yr.	Bilateral hernia; scoliosis; deformity of chest	..
87	44	20 yr.	Pans ¼ yr.	Pan feeder	Colliery road 8 yrs.; county council labourer 2 yr.; Army, India 5 yr.	Nil	II
88	44	1 yr.	Slack wheeling and kilns	Slack wheeling and kilns	Colliery screens 2 yr.; wool factory 3 yr.; foundry labourer 1 yr.; unemployed 1 yr.; laying pipes 1 yr.; Army (England) (A satisfactory occupational history was impossible to obtain in this case)	Bilateral varicose veins lower third pes cavus; chronic rhinitis	II

(*Continued on next page*)

TABLE 7—(*continued*)

No.	Age	Period in brick-works	Present occupation and how long	Principal occupation while employed in brickworks	Previous employment and how long	Defects	*X* ray class
89	45	3 mth.	Labouring, 3 mth.	..	Gentleman's service 9 mth.; Army, Home Service, Middle East, N. Africa, Italy, lorry driver 7¼ yr.; machinist and inspector 1 yr.	Deafness left ear; dry skin	..
90	46	24 yr.	Fitter, 24 yr.	Fitter	Machine shop, fitter 8 yr.	Emphysema both bases; keratosis right hand	II
91	46	7 yr.	Quarry labourer, 7 yr.	Quarry labourer	Colliery ganging 7 yr.; colliery coal face 15 yr.; erector 3 yr.	..	II+
92	49	1 mth.	Labourer	Labourer	Colliery trapping driving 3 yr.; Navy 4 yr.; bricklayer's labourer 5 yr.; engineering works, labourer 2 yr.	Near vision, J. 7, J. 7, J. 7; oral hygiene noted	V. Old rhonchi noted
93	51	23 yr.	Labourer, 23 yr.	Labourer	Woodyard labourer 2 yr.; colliery loading	Near vision (with glasses) J. 3, J. 8, J. 3; distant vision (without glasses) 6/36, 6/36, 6/36	II
94	51	8 yr.	Drawing	Drawing	Colliery screens 3 yr.; underground and surface and firing; odd jobs 1 yr.	Bilateral varicose veins; infected gums; occasional rhonchi	II+
95	54	2 yr. 6 mth.	Setting	..	Ginger beer factory 18 mth.; railway signal man 14 yr.; motor mechanic 2 yr.; agriculture 1 yr.	Nil	..
96	61	7 mth.	Kiln cleaner	..	Printing trade 6 yr.; public house 1 yr.; colliery surface 20 yr.; building trade 10 yr.; odd jobs	Left inguinal hernia; skin dry; low I.Q.; near vision (without glasses) J. 8, J. 8, J. 8; distant vision 6/18, 6/18, 6/18	..
97	63	29 yr.	Mixing	..	Shoe making 7 yr.; concrete sheds 9 yr.; Army, France, Home Service, 5 yr.	Bilateral inguinal hernia; exercise tolerance somewhat reduced	..
98	64	6 yr.	Labourer, 6 yr.	Labourer	Woodyard labourer 3 yr.; colliery bankman 9 yr.; colliery labourer 6 yr.; general labourer 13 yr.	Vision left eye near, J. 8; left eye distant 6/60	II
99	66	53 yr.	Burning	..	Army, N. Africa, Italy, Greece	Vision (without glasses) near J. 8, J. 8, J. 8; distant 6/36, 6/36, 6/36 (wears glasses)	
100	66	53 yr.	Burning	Burning	..	Vision (wears glasses for reading) near J. 8, J. 8, J. 8; distant 6/36, 6/36, 6/36	..

(3) the effect of undue changes of atmosphere and of noxious fumes among those working in the kilns and engaged in the cleaning of flues; (4) the possibility of ill health due to the arduous nature of the work.

Only fitters and workers engaged in taking green bricks off the press come into contact with mineral oil, while continuous work in a very dusty atmosphere is restricted to those operatives who maintain the flow of ground dust from the screens to the mixers. It is true that cleaning out the kilns and unloading them may also be dusty, especially in windy weather when the work may give rise to physical discomfort, but the workers do not stay in the kilns for many minutes at a time.

In the same way the exposure to sulphur dioxide given off in the kilns is intermittent. The only workers who are continuously exposed to sulphur dioxide are the men setting the green bricks. Our tests were carried out under favourable conditions and in no case did the concentrations reach one part in a million, a figure not substantially higher than is common in the atmosphere of industrial towns. We do not think that the concentration of sulphur dioxide is likely to exceed a few parts per million even in adverse circumstances.

The most striking features of these brickworks are (*a*) the absence of all forms of mechanized help in the operation of the kilns, and (*b*) the extreme changes of atmosphere which is the habit of workers in and out of the kilns.

From the time that the stiff plastic brick leaves the press it is handled four times before it leaves the brickworks. The green bricks are transported to the kilns by trolley and then stacked by hand at the rate of about 1,000 per hour. During unloading of the fired bricks these are stacked in fifties on a wheelbarrow and wheeled across the loading bay to waiting lorries. A man employed on this work averages 15,000 bricks per day: he thus makes 300 journeys per day, and each brick is handled twice. Wirecut plastic bricks are handled no less than six times, as they require to be dried before burning can take place.

Men are continually employed both in the hot chambers and out in the open air at regular intervals, and in winter weather extremes of temperature are considerable. The principal risks to health are the

monotonous and arduous nature of the work, as well as exposure to extremes of temperature.

An assessment of the physical condition of those entering the industry should therefore be carried out, and to do this a comprehensive medical examination is required. Candidates for employment giving a history of recurrent bronchitis and all those who admit to previous respiratory disease, whatever its nature, should be submitted to *x*-ray examination of the chest before a decision is reached as to their fitness for this type of work. Evidence of tuberculosis of the lungs, active or quiescent, must be regarded as a contraindication to employment.

People with a previous history of skin disease or actually suffering from dermatoses should be excluded if they are likely to come into contact with mineral oil, and attention should also be paid to the type of skin of such persons (Peters, 1944).

The placement examination is paramount in importance, but periodic examination of those exposed to the risk of skin affections should be undertaken every three months, and there should be annual *x*-ray examination of the chest in workers engaged in dusty operations of a continuous nature. As contact with mineral oil seems unavoidable in those taking green bricks off the presses, adequate washing facilities and the provision of a suitable barrier cream are essential to prevent the occurrence of dermatitis and keratotic changes in the skin.

The information about the environment and health of the brickmaker gained as a result of this survey serves to support, and in certain respects to amplify, that published in the Reports of the Committee on Amenities in the Brick Industry (1947). It also indicates the urgent necessity for implementing without delay the recommendations contained in that report.

Summary

A brief description is given of modern brick-making methods.

Environmental studies were carried out in a brickworks employing sixty-five workers.

These studies included a survey of atmospheric conditions, the dust hazards, the risk from exposure to fumes, and an investigation into the nature of the mineral oil in use.

In this survey it is shown that the dust hazard is not excessive; chemical analysis indicates that the material consists mainly of combined silica and alumina.

Traces of sulphur dioxide and hydrogen sulphide were found.

The carcinogenic properties of the mineral oil in use appeared to be low.

The general health of the workers was good. Seventy-three men had chest *x*-ray examinations; "dust changes" in the lungs were noted in two cases.

Two cases of keratotic changes in the skin were seen in workers who had been exposed to contact with mineral oil.

The number of accidents causing injury was very low.

Brick-making does not involve excessive occupational hazards, but it requires considerable physical effort and exposure to extremes of temperature is frequent.

Placement examination is essential to exclude those physically unfit for this work.

Periodic medical examination of certain workers is needed.

The recommendations in the Report of the Committee on Amenities in the Brick Industry should be implemented without delay.

Our thanks are due to the Directors of the Butterley Company Limited for permission to publish this article, to Mr. F. Catchpole, General Manager of the brickworks, for much help in the description of the technical processes; to Mr. E. R. Arnold of the *Derby Evening Telegraph* for the photographs illustrating brickmaking methods. We must thank Miss D. M. Pullon, Technical Assistant in the Medical Department, and other members of the Medical and Scientific Departments for assistance in the preparation of this paper. Mr. S. R. Cooper gave valuable assistance in the determination of toxic gases and examination of dust samples.

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BOOK REVIEWS

Archives de l'Institut de Médecine Légale et de Médecine Sociale de Lille. Published by Morel and Corduant. Lille. 1947. Pp. 255. Illustrated. No price given.

This number of the archives is devoted entirely to industrial medicine and contains articles by various contributors. The Institute is concerned primarily with occupational medicine in the four departments of this region. These have a population of 3½ million, of whom about 800,000 are engaged in industry. In recent years many doctors have taken the special course of study in industrial medicine in Lille, and the area contains a large number of doctors who are partly or wholly in industrial employment. It is served likewise by a technical and medical inspectorate of the government. The institute is equipped to carry out special research work.

In the course of a year about 20 per cent. of the labour force is involved in accidents at work and it would appear that though the accident service is well organized the professional skill of some of the surgeons, particularly those specializing in orthopædics or practising in this field without special knowledge, is subject to considerable criticism. One contributor thinks the time overdue for the status of a specialist to be more strictly defined and his professional attainments verified.

In the whole of France there is an active working population of about 12 million, and of these 600,000 are subject to accidents at work during the year and 2,000 people lose their lives in this manner. Accidents are increasing, though the reasons for this are obscure. It is apparently possible for owners of industrial undertakings to refuse entry to government inspectors desiring to verify working conditions.

There is great need of a comprehensive and easily understood handbook on safety and hygiene in industry. The present lack of such a handbook is particularly unfortunate as so many safety measures have to be understood and carried out by laymen.

Various industrial disorders are described in some detail. One contributor concludes that Dupuytren's contracture is not an occupational disorder but rather a diathesis, often hereditary. He differentiates from this the genuine occupational thickenings of the palmar aponeurosis, which are usually unilateral rather than bilateral. Another contributor describes a new method for the detection and estimation of arseniuretted hydrogen. A method of estimating olfactory acuity is also described.

A large number of the industrial workers in this part of France are engaged in the coal mines. Various detailed descriptions of the local rocks and coal measures are included in this volume, and one contributor thinks that the dust of a weathered rock is notably less injurious to the respiratory organs than dust from the same kind of rock which has not been exposed to weather. In his view, weathering occasions a metamorphosis of the rock structure.

Dust diseases are more frequent than before the war, but it is not clear whether this is an apparent increase due to better methods of detection. Aluminium powder as a preventive of silicosis is not advocated and is said to be contraindicated if tuberculosis is present.

Drs. Foubert and Nadiras have written an interesting article on a modified method of classifying individual aptitudes and occupational hazards. They have drawn on the experience of Eck, and under about twenty headings have devised a system somewhat reminiscent of Pulheems as now coming into use in the British Army. The results are seen in the form of a line drawn between various points on a table from above downwards. The items to be described are graduated from left to right in a series of horizontal lines one above the other. With practice it should be easy to read such a diagram very quickly and thus sum up both the man and the job.

Some attention is given to the legal position of a doctor employed in industry. By French law the employer cannot insure against inexcusable mistakes made by his employees, and among these are the doctor. Everyone guilty of such a mistake may be held directly responsible.

Although this volume is of considerable interest, regrets are expressed in the introduction that in many departments of industrial medicine France is still a long way behind other countries.

G. C. P.

Précis de Toxicologie. By U. Kohn-Abrest, Medico-legal expert for the Tribunal of the Seine. Paris. 1948. G. Doine et Cie. Second edition. Pp. 452; 70 figures. Price 980 fr.

The writer has in recent years investigated over three hundred cases of poisoning. Few of these were criminal, but there were seventy-eight cases of accidental poisoning, often by carbon monoxide, and twenty-nine cases of occupational intoxication.

In the chapter on gaseous poisons he gives a useful table of the relative toxicities of fumes from different types of motor vehicles and of various domestic heaters. In the third chapter he describes the effects of volatile poisons and notes that in cyanide poisoning the discovery of sulphur combined with cyanide is difficult of interpretation when autopsy is made some time after putrefaction has begun. In cases of alcoholic poisoning he also stresses the fact that death may occur when all traces of alcohol have disappeared.

In the post-mortem investigation of suspected cases of arsenic poisoning, error is sometimes possible unless the expert remembers that vestments and other articles enclosed in the coffin may yield some arsenic to the visceral remains. If intravenous arsenicals have been given they leave little trace, whereas subcutaneous arsenicals leave considerably more. If the viscera contain from 3 to 7 mg., arsenical treatment may still

be the cause, but if centigrammes are found then a more serious view should be taken.

Most of the common poisons are discussed, and the book is set out attractively. Having dealt with the inorganic compounds, the alkaloids, hypnotics, and other dangerous drugs, the author pays considerable attention to the use of physiological experiment to supplement other evidence. A useful description is also given of the whole course of an autopsy in a case of suspected poisoning. The case was imaginary, but is an excellent description of fatal cerebral hæmorrhage after a bout of alcoholism. *G. C. P.*

Silicosis Pneumokoniosis and Dust Suppression in Mines. London: Institution of Mining Engineers. 1947. Pp. 196; 23 plates. Price £1.

This book is an account of the proceedings of a Conference held in London in April, 1947. There were four sessions; broadly, the first was concerned with pathology, the second with therapy, the third with dust suppression, and the fourth with dust sampling methods; in fact in the first two the doctors were talking, and in the second two it was the turn of chemists and physicists. None of the papers contained new or original work, but the book is a valuable compilation in which good work published elsewhere is made readily available.

The outstanding paper of the first session was by Gough, in which he described his now well known views on simple pneumoconiosis with focal emphysema as the chief pathological change, and infected pneumoconiosis with progressive massive fibrosis in which he thinks tubercle is always present. In the second session the account of pneumoconiosis on the Kolar Gold Field in India, by Caplan, was the most important contribution, perhaps the most important contribution of the whole book, since a good description of the disease in India is not available elsewhere. It is far from clear why the lung changes in men working in this mining area, where drilling has to be done dry because of the heat and great humidity of the mines, should be so comparatively slight. Caplan suggests that it may be due to the large amount of silicates present in the dust. The valuable work of Craw has already been published in this journal. (*Brit. J. industr. Med.*, 1947, **4**, 30.) On the morning of the second day, the third session was devoted to papers on dust suppression methods on the Witwatersrand and in British coal mines, the principal methods used being good ventilation of the mines, the use of wet cutting methods, foam, and sprays for dust-allaying purposes. The last session was a highly technical one, in which the merits of the konimeter, the thermal precipitater, and other instruments used for dust sampling were discussed.

This is a useful publication which should be read by all who are interested in the subject of pneumoconiosis. *K. M. A. P.*

Textbook of the Rheumatic Diseases. Edited by W. S. C. Copeman, O.B.E., M.D., F.R.C.P. Edinburgh: E. and S. Livingstone. 1948. Pp. 612. Price 50*s*.

"The rheumatic diseases" is a vague term but one which has come into general use to cover a group of diseases affecting joints and muscles; and certainly a good textbook dealing with these diseases was badly needed. This book fulfills that want admirably. A book which has been written by twenty-four contributors is bound to have different styles and standards in it; but there is no doubt that some of the chapters in this book are of exceptionally high standard. The chapter on gout by Henry Cohen is an outstanding contribution. It is a model of how a chapter for a book of this type should be written, and it is complete with a full bibliography. Bibliography is important in a book which is designed, at least to some extent, to cater for the needs of postgraduates: and it is therefore a pity that in some chapters it is short and shows a tendency to refer to earlier textbooks rather than to original work.

The chapter on social and industrial aspects of rheumatism is ably written by William Tegner. He forcefully points out that there is no known ætiological relationship between occupation and this group of diseases, apart from the stress and strains of certain work which may accelerate the normal degenerative changes which Bauer has shown start in all human joints as early as the age of 21, and which finally give rise to osteo-arthritis. *K. M. A. P.*

Demonstrations of Physical Signs in Clinical Surgery. Part 2. By Hamilton Bailey, F.R.C.S., etc. 1948. Bristol: John Wright and Sons. Eleventh Edition. Illustrated. Pp. 95. Price 8*s*. 6*d*.

The second part of this book includes the description of the neck, breast, thorax, upper extremity, and herniæ, etc. All the sections are clearly illustrated in black and white and in colour; the herniæ and the neck lesions lend themselves well to photography.

The text is clear and concise throughout, so this edition should be as popular with students and practitioners as its predecessors have been. Students of industrial disease will look especially at the sections devoted to the upper limb, and particularly to those pages which describe injuries and infections of the hand. This part of the book could with advantage be enlarged in future editions. *E. C. B. B.*

BRITISH AND FOREIGN OFFICIAL PUBLICATIONS

Pilot Error : Some Laboratory Experiments. By D. Russell Davis, M.D., M.R.C.P., D.P.M., of the Applied Psychology Research Council of the M.R.C. 1948. Air Ministry A.P. 3139A. Pp. 39. Price 9*d.*

This forty-page monograph describes the results of tests carried out by pilots in the Cambridge cockpit testing machine, in which 355 pilots carried out a test lasting forty minutes. The Cambridge cockpit is a replica of the normal aeroplane, and the apparatus is designed to copy flying conditions with suitable changes in the readings of the instrument panel, and alterations in position of the cockpit, noise, etc., which accurately mimicked flying conditions. The test was divided into four ten-minute periods, and the movements of the levers by the pilot following the changes in the instrument readings were all plotted. The test was standardized, and about 75 per cent. were regarded as normal.

Those who were abnormal (87 subjects) were marked by two distinct reactions. Two-thirds were classified as showing the *overactive* reaction. Their movements to stabilize the plane, correct direction and height, etc., were rapid and excessive. They became irritable, and angry either with the machine or themselves ; they swore, and thumped on the controls, but seldom damaged the machine. They tended to concentrate upon one part of the problem, and neglected others. Those who showed this reaction returned later and wanted to do the test again, and they clearly showed an abnormal reaction to the procedure. The test had produced a post-experimental, too persistent, wrought-up feeling.

One third of the abnormal group showed an inert reaction. In the last period of the test these subjects' errors were large and the activity to correct the machine was small. There was a general omission of the necessary readjustments, but deterioration was selective and did not affect all parts of the test at once ; the instruments furthest away from the centre of vision were most neglected. They became indifferent, they lacked the appreciation of the changed readings which they should have shown, and they markedly underrated their own faults.

Both groups showed much worse reactions when they *knew* they were reaching the end, than when they did not. The abnormal subjects often showed preoccupation with one part of the task and were unable to organize their attention in such a way that they could attend to all the details at once. This apparent failure in behaviour was not associated with failure in the ordinary tests of intelligence, and surprisingly the author can find little justification for the belief that fatigue alone is the cause of failure.

There was good reason to believe that when it could be pointed out to the subjects what difficulties were likely to be encountered, and how these can be checked, the performance was improved. Results were impaired seriously by alcohol. Benzedrine in small doses gave conflicting results, but it did improve capacity after a sleepless night. The effects with barbiturates, caffeine, and vitamins were observed in some subjects. With the first two no conclusions were reached. With the latter, no alteration was produced despite large doses. *It was not found possible to explain the results on the theory of fatigue*, since no simple relation existed between frequency of errors and the duration of the test.

If fatigue cannot be incriminated, what explanation of the results can be given ? The author indicts " anticipatory tension," a process in all normal persons which lessens as success is gained. In the abnormal subjects the wish to succeed and the fear that they may not, result in the errors found. Confirmation of this was found in the study of the responses of thirty-nine patients, where the findings in the cockpit experiences were compared with the results of interviews with two independent psychiatrists, and where there was close correspondence between test results and subsequent flying career.

The application of these results to industry may seem small. Yet every factory has its overactive and inert persons, some of whom are problems when they are not actually accident-prone. It is seldom that matters of life and death weigh so heavily as in the conditions copied in the Cambridge cockpit. Yet such a study can hardly afford to be neglected, for several reasons. It confirms the doubts as to how far fatigue alone plays a part in accidents. It emphasizes human variables. It throws doubt on the efficiency of aptitude tests alone, divorced from the problem of the persistence of skill. We may find by the new tests the apt workman. Can we ensure so far as the delicate processes go that his skill will continue, or will he constantly be giving variable results because his performance can so seldom be relied upon ? Dr. Davis's paper should be studied alongside Grinker and Spielgel's *Men Under Stress*, a study of breakdown in U.S. airmen. The memorandum under review is very silent upon psychiatric problems and theory. But it does quietly emphasize how important these theories are, and it throws into commendable perspective the relationship between theory and the practical results which are presented.

This contribution from an academic psychological laboratory is an admirable survey. Is it too much to hope that bequests and grants should be given to quiet investigations of this sort, even though large-scale or immediate benefits are unlikely to follow ?

Henry Wilson.

Central Mining—Rand Mines Group. Report for the year 1947. By A. J. Orenstein. Johannesburg : Health Dept., Rand Mines Ltd. 1948. Pp. 18. No price given.

This is a statistical report on the native labour employed in the Rand mines. There are 91,108 natives employed and this labour showed a turnover during the year of 90·7 per cent. It is concerned with mortality rates, morbidity rates, food, the incidence of diseases in general, occupation, cost of hospital beds, and other such data. It states that silicosis does not play an important role in the health of native employees. This

is probably related to the large turnover mentioned above, the interrupted service, and the relatively low total years of service. In 1947, there were 58 cases (0·64 per 1,000) and 4 deaths (0·05 per 1,000). The pneumonia rate was 33·72 per 1,000, tuberculosis 2·39 per 1,000, and influenza 33·08 per 1,000. There were 12 cases of enteric fever, 22 of scurvy, and 2 of pellagra. There were 6 cases of heat stroke with 3 deaths.

K. M. A. Perry.

Legislacion Sobre Seguridad e Higiene del Trabajo. Published by the Spanish Ministry of Labour, with appendix for 1947. Pp. 202. No price given.

This volume deals with occupational safety and hygiene. It refers to legislation as early as 1900, from which date it would appear that the Spanish Government began to investigate and control industrial conditions more thoroughly than before. The book is in sections devoted to industrial accidents, including those occurring in agriculture or at sea. The insurance measures concerning these are also described, and the regulations designed to limit their incidence. Certain diseases are recognized as of occupational origin and are the reason for special precautionary and compensation legislation. The Ministry of Labour has a statistical department and also controls or suggests scientific investigation of accidents and occupational diseases. It has a staff of medical and lay factory inspectors, and appears to take particular care of women and children in industry. Their employment is completely prohibited in many occupations, and much restricted in others. There is special legislation to deal with women in the period before and after childbirth. This volume is not a complete description of all legislation, but rather a supplement describing recent additions or modifications thereof. The illustrated "safety first" posters are particularly well designed and worded. The worker's attention is drawn to the existence of a safety committee at his place of employment, and he is exhorted to keep in touch with it for mutual advantage.

G. C. Pether.

ABSTRACTS

(This section of the JOURNAL *is published in collaboration with the two abstracting Journals, Abstracts of World Medicine, and Abstracts of World Surgery, Obstetrics, and Gynæcology, published by the British Medical Association. The abstracts are divided into the following sections : toxicology ; industrial physiology ; industrial lung disease ; industrial dermatitis ; accidents and orthopædic surgery ; industrial opthalmology ; environment ; general. Not all sections will necessarily be represented in any one issue)*

TOXICOLOGY

Exposure to D.D.T. ANDERSON, A., and KHORRAM, M. A. (1948). *Brit. med. J.*, **1**, 1132.

A survey was made of 32 persons exposed more or less continuously for 9 months to DDT in oil. Sprayers who used 3 to 4% DDT in kerosene as a residual spray were liable to absorb the drug through the skin and by inhalation. Workers who used 2·5% DDT in a 75% gas-oil and 25% fuel-oil mixture for the control of mosquito larvæ were also liable to absorb the drug through the skin, as were the workers employed in mixing the two solutions. A comparison of the exposed group with a control group of 36 men in similar social circumstances and of similar nutrition (although of higher average age) revealed no difference in the average weight and blood pressure after the 9-month exposure. Vesiculation was observed in the sprayers where the straps of the spraying machine had chafed, but this was thought to be due to the kerosene. No significant signs or symptoms were noted in the exposed group, the recording of tremor of the hands in 9 men being regarded as doubtful. The urine of the exposed group was examined for organically bound chlorine but none was found, and it is suggested that this is not a reliable method for estimating absorption of DDT. It is concluded that the continued use of 3·1% DDT in kerosene, without protective clothing, is not likely to give rise to toxic effects. A plea is put forward for the use of a less noxious solvent than kerosene, or the increased use of emulsions of DDT.

Rachel MacHatton.

The Treatment of Acute Poisoning Produced by Gamma Hexachlorocyclohexane. MCNAMARA, B., and KROP, S. (1948). *J. Pharmacol.*, **92**, 147.

The high toxicity of the γ-isomer ("gammexane") of hexachloro*cyclo*hexane and the expected widespread use of it as an insecticide present possible poisoning hazards. Suitable treatment is suggested by the authors' findings that the marked hypertension and central stimulatory effects of gammexane do not occur in dogs given pentobarbital, and that gammexane action is antagonized by other isomers of hexachloro*cyclo*hexane. In addition, the structurally related *i*-inositol (hexahydroxy*cyclo*hexane), which is a growth factor for certain yeast strains, is known selectively to antagonize the toxic effect of gammexane on certain yeast strains. Massive dose of *i*-inositol administered prophylactically to rabbits over prolonged periods before the administration of lethal doses of gammexane (6 mg. per kg.) failed, however, to lower the mortality significantly.

The prophylactic intravenous administration to rabbits of 20 mg. per kg. of pentobarbital markedly reduced the toxicity of gammexane given intravenously, and afforded protection against 10 times the lethal dose. [Phenobarbitone is also stated by the authors in their comment and conclusions to be effective against the intravenous toxicity of gammexane.] The antidotal value of the α, β, and δ isomers of gammexane is much inferior to that of pentobarbital.

Gammexane administered orally to rabbits in the form of a 10% solution in peanut oil produced in 30 minutes to 4 hours symptoms qualitatively similar to

those after intravenous administration. A dose of 200 mg. per kg. was uniformly lethal, and this dose was used throughout the experiments. Under these conditions the therapeutic barbiturate (pentobarbital or phenobarbitone) was administered whenever convulsions occurred. [Route and dosage not stated.] Treatment with pentobarbital over 5 hours failed to protect any of 5 rabbits, but therapy over 32 hours protected 10 out of 11 rabbits treated with pentobarbital and 13 out of 15 rabbits treated with phenobarbitone. After treatment ceased, 8 additional rabbits in the pentobarbital group and 5 in the phenobarbitone group died. Pentobarbital had a rapid effect of short duration, and phenobarbitone gave lasting protection in doses causing less depression then pentobarbital.

The oral administration of gammexane to dogs produced a toxic syndrome similar to that in rabbits, and a lethal dose of 200 mg. per kg. was given to 8 dogs, which were treated symptomatically, usually by the intravenous route. Four out of 6 dogs treated with initial total doses of 30 to 65 mg. of pentobarbital per kg. and later doses of 10 to 15 mg. per kg., over a period of 4 to 5 days, became normal. A massive dose (125 mg. per kg.) failed to protect 1 out of 2 dogs treated intravenously with phenobarbitone. The second dog received 75 mg. of the drug per kg. and became normal in 3 days.

A suitable therapeutic regime suggested by these experiments is the administration of a small dose of phenobarbitone with subsequent symptomatic doses of a short-acting barbiturate to control violent convulsions. Artificial respiration and cardiac massage are also recommended. The persistence of toxic effects for several days after oral administration of gammexane, compared with the short duration of the effects after intravenous injection, suggests the possibility of hepatic storage and emphasizes the need for continued treatment with an appropriate depressant. No permanent functional injury was observed in animals which recovered as a result of therapeutic treatment. *J. Williamson.*

The Physiological Response of Experimental Animals Following Absorption of 2-Aminothiazole. DEICHMANN, W. B., KITZMILLER, K. V., HEYROTH, F. F., and WITHERUP, S. (1948). *J. industr. Hyg.*, **30**, 71.

In the synthesis of sulphathiazole, 2-aminothiazole is used as an intermediate compound; the potential risks of contact with this compound and of its inhalation suggested the need for toxicological investigation. Tests were made on albino rabbits and on guinea-pigs, rats, and cats. The compound, suspended in milk or olive oil, was introduced into the stomach of rabbits and cats by means of a syringe and a rubber catheter. For a single dose the LD 50 ranged from 0·12 g. per kg. in guinea-pigs and cats to 0·48 g. per kg. in rats, with an intermediate figure for rabbits. An increased rate of respiration was observed, with bodily weakness, diminished blood pressure, and mild convulsions. Animals usually died after 8 to 18 hours. There was an irritative action on the mucous membranes of the stomach and upper jejunum, and parenchymal lesions appeared in heart, liver, and kidneys. In the investigations on cumulative action, each of 5 rabbits was given 30 oral doses of 0·15 g. per kg., spread over a period of 56 days. The urea-nitrogen level in the blood rose slowly, and the ratio of organic to total sulphates in the urine increased. The application of the dry compound to the skin of rabbits and guinea-pigs for 2 hours on each of 30 days induced no signs of irritation of the skin. However, post-mortem examination disclosed the presence of microscopic lesions, proving the absorption of the powder.

When 2 rabbits and 6 rats were subjected to the inhalation of air containing 0·2 mg. of the compound per litre for 7 hours a day on 43 days, they suffered no apparent ill effects. Of a group of 5 guinea-pigs exposed to air containing 0·025 mg. of the compound per litre for 7 hours a day on 42 days, 2 died (after 4 and 41 days respectively), but the others survived without apparent illness. These tests suggest that harm to industrial workers can be avoided if care is taken to limit the dust content of the air. *H. M. Vernon.*

Porphyrinuria in Lead-poisoned Dogs. SALOMON, K., and COWGILL, G. R. (1948). *J. industr. Hyg.*, **30**, 114.

The authors investigated the effects of lead poisoning on porphyrinuria and certain blood conditions in dogs. Animals were fed on a diet low in iron-porphyrin-containing constituents, to which lead acetate was added. One of the 4 dogs under observation was used as a control. The urine was collected over periods of 9 or 10 days and kept under toluene. Porphyrins were extracted by Dobriner's modification of Hans Fischer's extraction procedure and were determined quantitatively with an Evelyn colorimeter. No stippling of the erythrocytes was observed. It was found that urinary coproporphyrin excretion increased considerably in a puppy after 40 days' exposure to lead, and remained high for 3 weeks. In two adult dogs the hæmoglobin level remained constant for 140 days, and then fell by 50% or more. Increased lead values in the blood (from 58 to 63 μg. per 100 ml. in one dog and from 41 to 99 μg. in the other) were observed after 2 months of lead ingestion. The excretion of porphyrin in these dogs fluctuated considerably for the first 70 days, and then, in one dog, the coproporphyrin excretion gradually rose to 1,080 μg. In the other the value did not increase for 150 days, and then rose abruptly to 1,100 μg. in the last 10-day period before death. It appears that, in dogs, porphyrinuria is a late rather than an early sign of lead exposure. *H. M. Vernon.*

The Physiological Response of Animals to 2-Aminodiazine and 2-Amino-4-Methyl Pyrimidine. TREON, J. F., WRIGHT, H., KITZMILLER, K. V., and YOUNKER, W. J. (1948). *J. industr. Hyg.*, **30**, 79.

The two substances 2-aminodiazine and 2-amino-4-methyl pyrimidine, are intermediate compounds which, when made to react with acetyl sulphanilyl chloride, yield, on subsequent hydrolysis, the sulphonamides sulphadiazine and sulphamerazine. When 2-aminodiazine was administered intravenously to rabbits as a 20% aqueous solution, the minimum lethal dose was found to lie between 0·5 and 0·8 per kg.; for oral administration to rabbits or guinea-pigs it was 0·42 to 0·62 g. The corresponding dose of 2-amino-4-methyl pyrimidine for rabbits was 1·17 to 1·40 g. The lethal dose of 2-aminodiazine was 2·16 g. per kg. for rats, and of the pyrimidine compound, 1·88 g. per kg. The poisoned rabbits and rats breathed with difficulty and died in from 2 to 49 hours. No evidence of cumulative effect was obtained when 50 sublethal doses (0·08 g. per kg.) of the 2-aminodiazine or (0·127 g. kg.) of the pyrimidine compound were administered at daily intervals on 6 days a week.

Rabbits were found to survive repeated skin applications of 2 g. of dry pulverized 2-aminodiazine or of 6 ml. of a 10% aqueous solution. Rabbits, guinea-pigs, and

rats survived intermittent inhalation of the compound in the form of dust (0·26 mg. per litre of air) or of vapour in the concentration of 0·077 mg. per litre. When given orally the compound caused superficial corrosion of the gastric mucosa and irritation of the upper portion of the jejunum in rabbits, guinea-pigs, and rats. while the liver and spleen were severely damaged. When a single lethal oral dose of the pyrimidine compound was administered to rabbits and rats, varying degrees of gastro-intestinal injury, and acute changes in the heart and liver, developed. There was also pulmonary congestion, due to direct vascular injury, and pneumonia frequently supervened. The proportion of organic to total sulphates in the urine of rabbits increased after administration of a single oral dose. A similar result was obtained with the 2-aminodiazine. In the manufacture and handling of the two substances mentioned there does not seem to be an undue industrial risk.

H. M. Vernon.

The Comparative Toxicity of Cryolite for Rats and for Rabbits. LARGENT, E. J. (1948). *J. industr. Hyg.*, **30**, 92.

The effects of natural cryolite and synthetic cryolite were compared and the rate of elimination of natural cryolite determined. Aqueous suspensions of cryolite were introdúced into the stomach of rats through a blunt metal tube, and into the stomach of rabbits through a rubber catheter. Rats were found to survive exceedingly large doses (up to 80 g. per kg.) of natural and of synthetic cryolite. This must have been due to the rapid elimination of the cryolite from the digestive tract. On the other hand, rabbits were killed by the administration of 9 to 12 g. per kilo of cryolite ; this seems to have been due to partial retention of the cryolite for a much longer period within the gas.ro-intes inal tract. The concentrations of fluoride in the blood of rats to which 16 g. per kg. of cryolite had been administered were much lower than those found in the blood of rabbits given either cryolite or sodium fluoride. Observations suggested that synthetic cryolite may be slightly more toxic than the natural mineral. *H. M. Vernon.*

Observations on Hydrazoic Acid. GRAHAM, J. D. P., ROGAN, J. M., and ROBERTSON, D. G. (1948). *J. industr. Hyg.*, **30**, 98.

Hydrazoic acid (azoimide), HN., is a weak acid. It is highly explosive, and is stated to be a severe protoplasmic poison. The authors carried out a clinical investigation on 10 workmen who had been exposed to hydrazoic acid fume for 1 to 15 years at a lead azide plant. Tests made in the area of maximum exposure showed the concentration of the hydrazoic acid to range from 0·3 to 3·9 parts per million. The men sometimes experienced headache, palpitations, and weakness, but quickly recovered on cessation of exposure. Exposure to hydrazoic acid in the concentrations encountered caused a rapid and severe fall of systolic and diastolic blood pressures which might persist throughout the shift. Previous investigators found that hydrazoic acid is extremely toxic to lower animals. The authors made tests on mice, rats, guinea-pigs, and rabbits, and found that lethal doses, when administered by injection or inhalation, caused irritation of the mucous membranes and excessive salivation, stimulation of the central nervous system, and a profound fall of blood pressure. Sublethal doses caused marked stimulation of respiration, with generalized convulsions. In white mice the LD 50 was found to be 21 mg. per kilo for hydrazoic acid, and 18 mg. per kilo for sodium azide.

H. M. Vernon.

Partition Coefficients of Fifty Compounds between Olive Oil and Water at 20° C. MACY, R. (1948). *J. industr. Hyg.*, **30**, 140.

According to the Overton-Meyer theory, the narcotic activity of a substance runs parallel with its ability to dissolve in fats. Since it is not practicable to measure directly the partition coefficient between the lipoids and watery fluids of an animal, a substitute oil-water system such as olive oil-water is generally employed. In the present investigation about 15 ml. of oil were placed in a 100-ml. flask, together with the organic compound and about 35 ml. of water, all three components being weighed in. The flask was placed in a constant temperature bath and rotated on its vertical axis at a speed of 1,000 r.p.m. for 6 to 60 hours. A sample of the water layer was withdrawn by pipette and run into the cell of a Zeiss " water " interferometer, where the concentration was determined. In all cases the measurements were made over a range of concentrations, and these are recorded in a table in detail, along with the mean partition coefficient and the extreme coefficients observed. The numerical data obtained in a representative experiment are also recorded. *H. M. Vernon.*

Hæmoglobin and Cytochrome C Metabolism in Experimental Lead Poisoning. (Zum Hämoglobin-und Cytochrom-c-Stoffwechsel bei der experimentellen Bleivergiftung.) PRADER, A. (1948). *Schweiz. med. Wschr.*, **78**, 273.

Lead disturbs the formation of hæmoglobin by interfering with the linking up of iron to the porphyrin ring. In experimental lead poisoning in the rabbit anæmia is associated with raised serum iron values and an increased excretion of porphyrin. Similar disturbances of porphyrin metabolism, and the failure of hæmoglobin formation from iron in both iron-deficiency and infective anæmias, led to the supposition that inadequate hæmoglobin formation is also the result of deficient linking-up of iron in the formed porphyrin molecule. Cytochrome-C synthesis takes place in all living aerobic cells, independently of hæmin formation in the bone marrow, and is not interfered with in lead poisoning. On the contrary, increase in cytochrom values in the tissues suggests a general increase in respiratory enzymes. This is not a feature peculiar to lead poisoning but is a general tissue reaction to inadequate oxygen supply. It is present in most anæmias as a compensatory mechanism for the partial deficiency in hæmoglobin. *Harold Jarvis.*

Pathology of Skeletal Muscle. (Zur Pathologie der Skelettmuckulatur.) HEDINGER, C. (1948). *Schweiz. med. Wschr.*, **78**, 145.

Two cases of damage to skeletal muscle after carbon monoxide poisoning are reported. A 21-year-old waitress was admitted to hospital unconscious and exhibiting a diffuse swelling of her right forearm with erythema and vesicle formation, resembling a first-stage burn. The swelling was strictly confined to an area which had been exposed to pressure by a bracelet. Traces of albumin were found in the urine on the first day only. During the following days sensibility of the right hand was impaired, but these changes as well as the condition of the skin improved gradually. One month

after the accident, however, contracture of the right hand developed; this resembled Volkmann's contracture and necessitated surgical intervention. At operation scar tissue around the median nerve and in several flexor muscles of the forearm was removed. Biopsy revealed chronic myositis with atrophy and waxy degeneration. The second case was that of a 30-year-old mason, who remained unconscious for 3 days after severe accidental coal-gas poisoning. From the tenth day onwards a painful swelling of the gastrocnemius developed, measuring about 7×2 c.m., in which 7½ months afterwards numerous small calcareous bodies were demonstrable radiologically. The skin was not affected. The condition was held to be one of calcification of the calf muscle after muscle necrosis due to carbon monoxide poisoning.

The author traced 28 cases in the literature and outlines the following entity. After severe carbon monoxide poisoning there is transient albuminuria (rarely glycosuria), and in those parts of the body which have been exposed to pressure a triad may develop consisting of skin damage and loss of sensibility and motility. The former resembles a burn. The sensibility is reduced distal to the skin lesions. Involvement of the muscles is shown by paralysis, swelling, and pain, and leads to permanent damage—paralysis, atrophy, contracture, calcification. Infection of gangrenous skin and underlying muscles may occur, with subsequent death. Biopsies show hyaline, fatty, or waxy degeneration of muscle, with some inflammatory reaction and occasional hæmorrhage, and calcification and scar formation in the later stages.

The author suggests that muscle damage after carbon monoxide poisoning is not toxic in nature, but occurs only when compression—possibly mechanical hyperactivity—is a superadded feature and is the cause of a locally insufficient blood supply. In some cases albuminuria, myoglobinuria, oliguria, and death due to uræmia have been reported. It is deduced that extensive muscle damage due to carbon monoxide poisoning may produce the complete clinical and histological picture of the crush syndrome.

R. Salm.

Pathogenesis of Cerebral Changes in Acute Carbon Monoxide Poisoning. (Sulla eziopatogenesi delle alterazioni dell'encefalo nella intossicazione acuta da ossido di carbonio.) CERESA, C. (1948). *Med. d. Lavoro*, **39**, 19.

The brains of two persons dying from carbon monoxide poisoning were examined. One had died after 26 days, and the other after 1 day. The latter was a child of 5 who, with its mother, had been poisoned by coal gas. At necropsy sections were taken from various parts of the brain and morbid changes were observed in the cortex and the bulb. Hyaline thrombi were seen in the capillaries and small veins; there was no perivascular exudation but the brain was œdematous. The oligodendron cells were swollen and rounded; the cytoplasm was transparent and the nucleus displaced towards the periphery, its processes being shortened or absent. These changes were easily recognized by the silver staining process of Schültzer-Orlandi. There were no appreciable changes in the neuroglia or in the nerve cells. The pathological changes in the vessels in the first case were similar, but the nerve cells had suffered considerably. The author did not observe the fatty degeneration of the endothelium or of the parietal layers described elsewhere. Nevertheless, in his first case the nerve cells had changed in shape from pyramidal to ovoidal, the outlines were blurred, the cytoplasm was reduced, and the Nissl bodies had disappeared or were at the extremity of the cells. The nucleus was vacuolated and had no nucleolus, with scanty chromatic substance and often a peripheral location. The neurofibrils were granular and the cylinder axes varicose and fragmented. The neuroglia was increased in quantity. The author considers that the vascular injury occurs first, and that the subsequent changes are due to this.

G. C. Pether.

Problems of Generalized Clinical and Experimental Argyrosis. (Problemi dell'argirosi generalizzata umana e sperimentale.) ROMUALDI, G., and CORTESI, C. (1947). *Arch. "De Vecchi" Anat. pat.*, **10**, 189.

For experimental purposes 6 rabbits of equal weight were used. Two received nasal instillations twice daily of a 4% solution of silver nitrate, the first being killed 40 days after such treatment, the second after 3 months. The second pair received nasal instillations of a 5% solution of "argyrol." The first was killed after 2½ months' treatment, the second after 4 months. The third pair received nasal instillations of a 6% solution of "protargol." Both animals were killed 4 months after the treatment had started. One was exposed to sunshine for about 8 hours per day during the month of August. On histological examination mainly quantitative differences were found. However, the metallic granules in the first pair were mostly extracellular, while in the second and third pairs they were mostly taken up by the cells of the reticulo-endothelial system. Exposure to sunlight had no effect.

The authors observed a woman, 79 years of age, who had received silver-nitrate eye drops for some unknown disease 40 years before she was admitted to the hospital. After she had been using these for 6 months she became pigmented in the face, neck, arms, and higher parts of the abdomen. She was admitted to the hospital for bronchopneumonia, from which she died. At the post-mortem examination her organs were found to be affected by argyrosis. The histological examination of kidneys, thyroid gland, lymph nodes, skin of the face and abdomen, and common carotid artery showed metallic granules inside and outside the parenchymal cells. Chemical examination confirmed the fact that these granules consisted of metallic silver.

According to the authors, absorption of silver is mainly through the blood, less through the lymphatic system. This would explain the finding of considerable quantities of silver in the renal vessels and its deposition in the perivascular tissue. There is a large amount of silver in the skin, mostly in places exposed to friction. The role of the reticulo-endothelial system in the genesis of argyrosis is still doubtful. The authors believe that the silver is taken up at the site of administration by the reticulo-endothelial system; only if this system is less active than usual can general argyrosis result. Further, the development of generalized or localized argyrosis depends on the behaviour of the reticulo-endothelial system. The reticulo-endothelial system may be constitutionally weak, or may be damaged through the toxicity of the silver compound. Thus occupational argyrosis from silver nitrate often becomes generalized because of the toxicity of this compound. The toxicity could be demonstrated in the experiments with rabbits treated with silver nitrate; in contrast to the others these animals lost weight.

E. Forrai.

INDUSTRIAL PHYSIOLOGY

The Effect of Food Supplements on Poorly Fed Workers in Brussels in January 1945. SMART, G. A., MACRAE, T. F., BASTENIE, P. A., and GREGOIRE, P. E. (1948). *Brit. med. J.*, **1**, 40.

Two groups of men working in Brussels, who in 1945 were receiving inadequate food were given a supplement mainly of milk, cheese, butter, and eggs. After a control period Group A received the supplement for 10 days, Group B acting as controls; after 3 weeks the groups were reversed and the supplement was altered slightly. Body weight, strength of grip, myotatic irritability, and urinary nitrogen excretion were determined. During supplementation there was a significant increase in body weight, strength of grip, and urinary nitrogen excretion, and a significant decrease in myotatic irritability. There was no significant relation between the individual measurements of different factors or between the measurements and the intake of any particular nutrient. There was initially an inverse correlation between strength of grip and myotatic irritability. It is pointed out that the increase in strength of grip may have been caused by the psychological factor, since the workers knew whether they were receiving the food supplement or not. [For assessing the results on myotatic irritability it would have been helpful to have had measurements of the thickness of skin and subcutaneous tissue, since an increase of subcutaneous fat will decrease the stimulus actually applied to the muscle. It is interesting that in the underfed workers in Group B after 10 days of supplementation myotatic irritability was less than in average "healthy R.A.F. subjects."]

The urinary nitrogen excretion is discussed in detail. During the period of supplementation the excretion of nitrogen by those given the supplement and by control subjects is stated to have increased significantly; the mean excretion in the two groups was [surprisingly] the same. [On the figures published, the increase in the control group is not significant: the mean before feeding is $9{\cdot}5 \pm 1{\cdot}3$ (s.e.) and after feeding is $10{\cdot}8 \pm 0{\cdot}03$, and the difference between the means is only 1·05 times the s.e. of the difference; the mean for the group just before the experimental period is 10·74 and at the end of the experimental period is 10·57. It is difficult to place much reliance upon the figures for nitrogen excretion, since the results obtained in 3 of 18 subjects were omitted because "the 24-hour specimens of urine presented by them were obviously false"; other samples may have been false but not obviously so. There is, for instance, a significant difference in the scatter of the values for mean nitrogen excretion of the control group before and during the experimental period, although there was no alteration in their type of diet during the experimental period.] *H. M. Sinclair.*

Ventilation of Clothing and Tolerance of Man to Low Environmental Temperatures. HORVATH, S. M. (1948). *J. industr. Hyg.*, **30**, 133.

The ability of man to tolerate low temperatures is influenced by the provision of convenient ventilation of the garments, so that the effects of excessive sweating during work can be avoided. Tests were made on 10 soldiers to determine the adequacy of the garments in preventing the accumulation of sweat during work, and the thermal exchanges through the garments when the subjects were at rest. At a temperature of −23° C. the men walked on a motor-driven treadmill up a 3% gradient at a speed of 3·3 miles (5·3 km.) per hour. In different tests the men (*a*) wore their clothes completely closed at all times; (*b*) opened up the clothing as much as possible without discarding garments; and (*c*) removed garments as necessary to prevent themselves from becoming overheated. In many tests the subjects wore 2 windproof garments, 1 outside and 1 inside the pile garments. The average weight loss (corrected for evaporation of water from the lungs and for carbon as carbon dioxide) was 333 g. per hour when the clothing was tightly closed, and 173 g. when it was discarded at will. When ventilation was permitted by opening garments, the results obtained were variable, the average loss being 240 g. Men who had accumulated moisture as a consequence of work could sit quietly for brief periods immediately afterwards, but were more susceptible to cold exposure if the clothing was worn on a succeeding day without being dried. Numerical details of the weight changes in separate items of the clothing worn are given. *H. M. Vernon.*

The Influence of Clothing, Work, and Air Movement on the Thermal Exchanges of Acclimatized Men in Various Hot Environments. NELSON, N. A., SHELLEY, W. B., HORVATH, S. M., EICHNA, L. W., and HATCH, T. F. (1948). *J. clin. Invest.*, **27**, 209.

Three acclimatized men were subjected to seven different environmental temperatures ranging from 90° to 120° F. The partitional calorimetric approach was used; this method allowed a quantitative description of thermal exchanges in these hot environments. The responses in relation to clothing, work, and air movement were noted. At each of the temperatures studied, wind velocities of the order of 30, 75, 150, 300, and 600 feet per minute (approximately) were developed and the following physiological responses noted—rectal temperature, skin temperature, surface temperature, sweating and pulse rate. It was concluded that (1) metabolic heat production for a given amount of work remains unchanged irrespective of change in environmental conditions, (2) in the resting state a fully-clothed man gains less heat and consequently there is a smaller evaporative-heat loss, (3) convective- and radiant-heat gain and the compensatory evaporative-heat loss show a progressive increase with increasing air movement.
A. I. Suchette-Kaye.

A Study of the Mechanism and Treatment of Experimental Heat Pyrexia. DAILY, W. M., and HARRISON, T. R. (1948). *Amer. J. med. Sci.*, **215**, 42.

In health a level body temperature is maintained by a delicate mechanism whereby excessive biochemical heat production or exposure to inordinate heat is counterbalanced by appropriate physical heat loss, mostly in the form of sweating. Three forms of heat stroke may be recognized—simple exhaustion or prostration, painful cramps, and spasms of the skeletal muscles and a severe condition marked by hyperpyrexia, coma, convulsions, bounding pulse, and hot, dry skin, the patient passing into a state of vascular collapse, tissue anoxia, and pulmonary œdema. This third manifestation is best described as "heat pyrexia" or heat stroke proper. The outstanding danger to a person exposed to excessive heat is any impediment to sweating or any cessation of that process. The essential and cardinal requirement for a patient overcome by heat pyrexia is a rapid reduction in temperature, and this can be attained by wrapping the patient in wet sheets and playing cool streams of air on them with electric fans. The authors of the present

article, however, cite experimental and clinical evidence purporting to show that reduction of hyperpyrexia is most satisfactorily and safely attained by immersion of the patient in ice-cold water. *G. F. Walker.*

INDUSTRIAL LUNG DISEASE

Studies on Aerosols. I. Reduction of Dust Deposition in Lungs of Rabbits by Aqueous Aerosols. DAUTREBANDE, L., HIGHMAN, B., and ALFORD, W. C. (1948). *J. industr. Hyg.*, **30**, 103.

Tests on the effects on aerosols were made with series of 1 to 3 rabbits exposed for 5 hours in a cage of 280-litre capacity. The air in the cage was mixed with aerosol (0·1% aqueous solution of "aerosol O.T."), which was dispersed by a generator producing per c.mm., 500,000 liquid particles averaging 0·5 μ in diameter. A control test was made at the same time without aerosol, the source of the dust in each case being willemite, a zinc silicate. This substance fluoresces a brilliant green in ultra-violet light so that particles of even less than 1 μ can be detected in tissue sections after the organic matter has been destroyed by micro-incineration. The dust generator produced particles averaging 0·9 μ, the dust concentration averaging 0·01 to 0·04 mg. per litre of air in a continuous flow of 60 litres per minute.

The rabbits breathed irregularly and were cyanosed after 2 hours' exposure to dust without aerosol, but these signs were absent in those exposed to dust together with aerosol. The lungs of some of the rabbits were removed after death and fixed in formalin, and the paraffin sections were ashed by heating to 450° C. for 4 hours. They were examined under reflected ultra-violet light of 2,537 Å; the sections from rabbits exposed to dust and aerosol contained much less dust than those exposed to dust only, especially in the alveolar ducts and alveoli. The dust in the parenchyma also appeared to be much less. The aerosol appears to coat the particles of dust, agglutinate many of them, and thereby increase the diameter of the inhaled particles. Their pulmonary penetration is therefore impeded. *H. M. Vernon.*

Studies on Aerosols. II. Coating and Agglutinating of Dust Particles by Aqueous Aerosols. DAUTREBANDE, L., ALFORD, W. C., and HIGHMAN, B. (1948). *J. industr. Hyg.*, **30**, 108.

In order to test the effects of aqueous aerosols on minute dust particles suspended in the air, finely-ground quartz or willemite particles were generated from distilled water or an aqueous solution of eosin Y, by an air current of 50 litres per minute. Samples of the particles of aerosol, dry untreated dust, and aerosol-treated dust were collected, by sedimentation in a chamber, on microscope slides coated with vaseline. They were measured by means of an oil immersion objective magnifying 1,125 times. The size of most of the aerosol particles was 0·8 to 0·4 μ, and of the quartz particles, 1·0 to 0·5 μ. In one test, when the dust-laden air stream was mixed with aerosol, all the particles collected by sedimentation were found to be coated with water, their mean diameter being increased from 0·95 to 1·41 μ. The cumulative size was still greater in some other tests. In an experiment with willemite dust (fluorescent zinc silicate) the aerosols were produced from 5% eosin, and the size of the exposed particles was increased from 1 μ to 2·7 μ. In an experiment in which a more elaborate apparatus was used, the aerosol-treated dust had a diameter of 1·3 μ compared with one of 0·62 μ for the dry dust. When quartz was used in place of willemite the mean diameter was increased from 0·7 to 2·3 μ. In these tests there were many aggregates of dust particles of larger diameter, usually exceeding 3 μ, and occasionally even 20 μ.

These experimental results suggest that aerosols may be found useful in supplementing current methods for the control of dust hazards in occupations where large amounts of fine dust are dispersed.

H. M. Vernon.

A High Volume Air Sampling and Filter Weighing Method for Certain Aerosols. SILVERMAN, L., and VILES, F. J. Jr. (1948). *J. industr. Hyg.*, **30**, 124.

In this investigation a compact cellulose pleated filter was used. It was 3 inches in diameter, had a pleat height of 1 inch, and it gave a surface of 84 square inches. It is available commercially. It was contained in a high-volume sampler, having a sampling cone, spider web, and filter-retaining ring; also a manometer, which showed a pressure drop of 15 in. of water at 60 c.f.m. The housing of the apparatus contained an Electrolux blower (535 watt motor). The relative efficiency of the filter was determined by using two filters in series, and absolute efficiencies were obtained by using an electrostatic precipitator as a standard. Tests were made with dried silica dust less than 325 mesh, air-borne dust collected in cotton textile plants, and lead fume. The efficiency was always over 99% for these dusts, but with tobacco smoke it was only 59 to 68%.

The filters weighed from 8 to 10 g., but direct weighings gave irregular results owing to moisture absorption and adsorption. To eliminate most of the moisture gain, weighing should be done at a temperature above 100° C., in accordance with the method described.

H. M. Vernon.

The Aluminium Lung: A New Industrial Disease. (Die Aluminiumlunge—eine neue Gewerbeerkrankung.) GORALEWSKI, G. (1947). *Z. ges. inn. Med.*, **2**, 665.

The author suggests that the inhalation of any dust causes trouble only when other factors—climatic, dietic, and environmental—combine to injure the patient. Only on this assumption is it possible to understand why some individuals appear to be immune to the effect of dust inhalation. Despite arguments against his views the author claims to have incontrovertible evidence that aluminium dust may cause rapid and progressive morbid changes in the lungs. He has chosen the term "aluminium lung" to define most clearly the entity described.

He considers that the apparent recent increase in lung diseases due to aluminium dusts is attributable to a change in the process of manufacture. The aluminium powder sold under the name of "bronze powder" contained stearin, which had been added during the stamping process. But when aluminium was needed as a powder for military purposes the addition of stearin was no longer desirable. This explains the more frequent and serious cases of dust disease reported just before and during the war. Jäger believes that the aluminium particles protected by stearin do not penetrate the lung tissue as a solution but are taken up by phagocytes; without this protection solution readily occurs. The aluminium ion precipitates proteins and in this way attacks lung tissue, causing rapid destruction, distortion, and fibrosis. It is said that these changes may be distinguished from those due to coal, iron, stone, and asbestos dusts.

Estimation of the respiratory capacity, especially during work under a load, gave valuable information about the amount of damage caused by the dust. But even at rest the diminished respiratory reserve is often noted long before there are any radiological changes. The morbid changes do not occur in any clearly defined order, but there is rapid spread of diffuse hyaline degeneration with particular injury to the elastic tissue. It is difficult to distinguish in the radiograph the aluminium lung from one which is tuberculous, but spontaneous pneumothorax is common and the loss of elastic tissue produces characteristic distortions of the pulmonary and cardiac outlines. The macroscopic changes recorded are readily explained from examination of microscopical sections. *G. C. Pether.*

Pneumonoconiosis Due to Talc in the Cosmetic Industry. MILLMAN, N. (1947). *Occup. Med.*, **4**, 391–394.

Pneumonoconiosis resulting from talc (asbestine and tremolite) has been fairly extensively reported as occurring in miners and millers. This, however, is only the second case reported as developing in a man working on the manufacture of talcum powder. He was aged 55, and had for 24 years been employed in the talcum-powder mixing room of two cosmetic factories. He complained of pain in the chest and weakness. He was slim and underweight but had no abnormal physical signs. *X*-ray examination of the chest revealed nodular densities ranging from 1 to 3 mm. scattered throughout both lung fields and in both hilar regions, and a thickened pleura between the upper and middle lobes of the right lung. Dust counts showed 16,000,000 particles per cubic foot (0·028 cubic metre) of air in the general room atmosphere, 236,000,000 when the mixing machine was being filled, 133,000,000 while the pulverizer was operating. The powder contained less than 0·5% of free silica. The talc had added to it zinc stearate, osmokaolin, chalk, and colouring.

K. M. A. Perry.

Benign Pneumoconiosis Due to Tin Oxide. A Case Report with Experimental Investigation of the Radiographic Density of the Tin Oxide Dust. PENDERGRASS, E. P., and PRYDE, A. W. (1948). *J. industr. Hyg.*, **30**, 119.

A workman, aged 45, had for 15 years been bagging tin oxide dust obtained by treating tin cans with a caustic. The inhalation of the dust produced pseudo-nodulation in the lung fields similar to that seen in arc welders, and the authors named the condition benign pneumoconiosis. There was little fibrosis and never any true nodulation. The tin oxide dust contained 96·5% of tin oxide, but no silica. When an artery of a freshly excised dog's lung was injected with a saline suspension of tin oxide, or the suspension was instilled into the bronchi, even small amounts of it produced appreciable densities in the lung.

H. M. Vernon.

Pneumonokoniosis in New South Wales Coal Miners. NISBET, A. T. (1948). *Med. J. Aust.*, **1**, 389.

The coal mined in New South Wales is soft and has a silica content varying from 0·4% to 4·0% ; no anthracite is found in Australia. The average number of employees in New South Wales collieries between 1941 and 1946 was 17,600. The incidence of incapacitating pulmonary fibrosis due to dust was 4·90 per 1,000 employees per year (2·75 partly and 2·15 totally incapacitated). The earliest identifiable changes are of nodular fibrosis rather than reticulosis. Enlargement of the hilar and mediastinal lymph nodes is unusual in N.S.W., and it is unusual to find any evidence of tuberculosis. Linear fibrosis is common but is not by any means confined to coal-workers and cannot be taken as evidence of damage by dust. If much linear fibrosis is detected in the radiograph of a coal-miner, there is usually little or no sign of nodular fibrosis. From this the author concludes that the presence of chronic bronchitis is protective against the action of inhaled dusts, and suggests that the increased [inflammatory] secretions in the bronchi trap the dust particles, which are later expectorated. [This is an interesting observation, but it is doubtful whether workers elsewhere will agree that chronic bronchitis has a protective influence.] *H. E. Harding.*

Radiological Study of the Pulmonary Hilum in Silicosis. (Studio radiologico sugli ili polmonari nella silicosi.) ZANETTI, E. (1948). *Med. d. Lavoro*, **39**, 7.

The author examined 4,000 chest radiographs ; in 1,062 silicotic changes were observed. He divides the latter series into 600 with fibrous reticulation, 110 with fibrosis and early nodular changes, 240 with nodules, and 76 with massive silicosis. He considers that in nearly all cases with reticulation there is some visible silicotic change in the hila. The changes did not vary much with the source of risk. Marked involvement of the lower parahilar lymph nodes was noted in workers who gradually developed pathological changes due to persistent slight inhalation of dust. In most of the 1,000 cases there were some hilar changes. The common hilar changes characteristic of silicosis include symmetrical variations from the normal with enlargement, a more marked demarcation of the lower parts, and a "fluffy" border to the shadows. Hilar changes often precede the more widespread reticulation but, when the latter is marked and nodular areas appear together with patches of emphysema, the contrasting density of the hila is less obvious. In the differential diagnosis from tuberculosis it should be observed that the glandular changes in the latter are rarely symmetrical but are more clear-cut. *G. C. Pether.*

Clearing of *X*-ray Shadows in Welders' Siderosis. DOIG, A. T., and MCLAUGHLIN, A. I. G. (1948). *Lancet*, **1**, 789.

The authors first drew attention to welders' siderosis in 1936 (*Lancet*, **1**, 771). In the present paper they describe their findings when they re-examined 15 of the cases which were the subject of the earlier work.

Two had left their employment as welders ; *x*-ray changes had been observed in both in 1936, but in 1945 the radiograph in 1 case was normal and in the other the shadows had become less intense. Four men whose earlier radiographs had been abnormal were unchanged ; they had continued work as welders, but remained clinically well. The radiographs of 2 men were normal in 1936, but were classed as "suspicious" in 1945 ; 2 others who had been suspect in 1936 now showed reticulation. In the remaining 5 cases there were no abnormal *x*-ray changes in 1936 or 1945. None of the men had any clinical disability.

The sputum has been shown to give the Prussian-blue reaction for 18 months after exposure to dust ceases, and it is concluded that much of the dust is removed from the lungs in the sputum. Several workers agree that the condition does not cause disability and should be classified as a benign pneumoconiosis. *L. W. Hale.*

Fatal Pneumonia after Inhalation of Glass Dust During Preparation of a Synthetic Substance from Glass Wool. (Tödliche Pneumonie nach Glasstaubinhalation durch Verarbeitung eines Kunststoffes aus Glaswolle.) KAHLAU, G. (1947). *Frankfurt. Z. Path.*, **59**, 143.

An interior decorator, aged 67, fell ill after working for 5 weeks with an artificial material described as glass wool. A left-sided lobar pneumonia was diagnosed. At necropsy the principal findings were: (1) lobar pneumonia of the left upper lobe with many small abscesses; (2) encapsulated empyema; (3) purulent bronchitis; (4) bronchopneumonia of the right lower lobe; (5) fibrinous pericarditis. *Pseudomonas pyocyanea* was cultured from one of the abscess cavities. Microscopically, the right lobe showed the typical picture of acute bronchopneumonia, but the alveoli of the left upper lobe contained but few polymorphonuclear cells and were filled with fibrin and numerous histiocytes, which frequently incorporated small, clear, unstainable transparent bodies. The silica content of the lungs was not greatly increased (15% SiO_2 in the ashed tissues). This, according to the author, is not surprising, as the total quantity of inhaled glass dust must have been small. The diameter of over half of the inclusion bodies proved to be 10 μ (none was larger); this was also the diameter of the thread of the glass wool. The ashed lung and the glass wool both contained about 0·08 μg. (per cent.) of lead. These findings suggest that pneumonia was due to inhaled glass dust.

R. Salm.

Industrial Hygiene Aspects of the Cemented Tungsten Carbide Industry. FAIRHALL, L. T., CASTBERG, H. T., CARROZZO, N. J., and BRINTON, H. P. (1947). *Occup. Med.*, **4**, 371.

Cobalt, either as oxide or as metal, is an aerial contaminant at all stages of cemented tungsten carbide manufacture. The dust content of air in powder-processes averaged 3·5 mg. per cubic metre, of which 4·1% was cobalt. The authors examined 1,802 workers, the median ages being 33·8 years for men and 24·4 years for women. Of the total, 28% had worked for more than 6 years in tungsten carbide, and 57% between 2 and 5 years. In these workers there was an excessive incidence of disease of the upper respiratory tract and bronchopulmonary disease and also of abnormal findings on physical examination of the conjunctivæ. On *x*-ray examination 45 workers were found to have reinfection tuberculosis, a prevalence of tuberculosis of 2·5%. In 36 workers there were granular or conglomerate markings, but 64% of these had previously been employed in mining or in metal fabricating industries. Hæmatology, tests for syphilis, and tests for albuminuria and glycosuria revealed no remarkable changes. The incidence of arteriosclerotic-hypertensive heart disease compared favourably with that in other industries.

K. M. A. Perry.

Delayed Pneumonitis in a Beryllium Worker. Report of a Case. AGATE, J. N. (1948). *Lancet*, **2**, 530.

The handling of beryllium compounds is attended by risk of dermatitis and of respiratory disease. This is probably the first recorded case of beryllium pneumonitis in Great Britain but further cases may be expected. Prognosis is poor, treatment ineffective, and disability serious and permanent.

INDUSTRIAL DERMATITIS

The Production of Dermatitis by Pyrethrum and Attempts to Produce a Non-irritant Extract. LORD, K. A., and JOHNSON, C. G. (1947). *Brit. J. Derm. Syph.*, **59**, 367.

During the recent war a considerable proportion of the users of mosquito-repellent ointments containing pyrethrum extracts became sensitized to these preparations. After the war "some of the people thus sensitized were used as test subjects" for a cream containing "40% colourless concentrate of pyrethrum (commercial preparation)"; 6 of 62 men and 7 of 27 women who were tested became sensitive to the use of the cream. Further tests showed that the dermatitis-producing factor was in the pyrethrum extract, and experiments designed to produce a pyrethrum extract which would be free from this undesirable ingredient are described. It was known that preparations of high pyrethrin content could be obtained from petroleum extracts of pyrethrum flowers by chromatographic adsorption with columns of fuller's earth, and preliminary experiments suggested that the dermatitis-producing factor was more strongly adsorbed by the fuller's earth than was the pyrethrum. In view of these promising results, various modifications of this method of extraction were tried, and the resulting extracts were tested on persons previously sensitized to the commercial extract. The authors say, "From these results it can be inferred that petroleum ether and ethylene dichloride wash out the pyrethrins from a column of fuller's earth which retains the dermatitis-producing factor, but that ethylene dichloride does not seem to be such a promising solvent as petroleum ether for the operation. The removal of the colouring matters from petroleum ether extracts by activated charcoal does not appear to influence the removal of the dermatitis-producing factor from the solution of fuller's earth."

R. M. Gordon.

Eczematous Cross-hypersensitivity to Azodyes in Nylon Stockings and to para Phenylendiamine. DOBKEVITCH, S., and BAER, R. L. (1947). *J. invest. Derm.*, **9**, 203.

The authors conclude that the causal factors in the production of nylon-stocking dermatitis are the various azo dyes. The relation between nylon-stocking dermatitis and the dermatitis due to *para*-phenylenediamine, and the common chemical basis for the hypersensitivity are discussed and explained by the mechanism described by Mayer.

G. B. Mitchell-Heggs.

Studies of Sweating. I. Preliminary Report with Particular Emphasis on a Sweat Retention Syndrome. SULZBERGER, M. B., HERRMANN, F., and ZAK, F. G. (1947). *J. invest. Derm.*, **9**, 221.

In this interesting paper the authors show that in several of the common dermatoses there is interference with sweat secretion. This disturbance is most commonly seen in prickly heat, but similar plugging of the sweat glands occurs in a variety of conditions, such as atopic dermatitis (disseminated neurodermatitis), mild forms of ichthyosis or ichthyosiform erythroderma, and dry forms of seborrhœic dermatitis. When a sufficient number of sweat glands is firmly plugged, the affected patients have the following symptoms: Rapid elevations of environmental temperature accompanied by high humidity bring on attacks of pruritus. Systemic malaise may accompany the attack. Almost immediately after the rise in temperature, various types of skin lesions appear and may include papules, papulo-vesicles, and vesicles. The secretion of sweat is reduced or absent

in large or small areas. Sensible perspiration tends to occur on repeated stimulation in certain fixed regions. Reduction of surface sweat is due to the plugging of the orifice of the sweat duct. More or less prompt subjective relief and objective improvement follow consistent reduction of environmental temperature and humidity. Improvement also follows local procedures which cause shedding of the plugs, and measures which reduce the tendency to sweat.

Cases illustrating these points are described, and the authors also give in detail 2 cases of post-mepacrine lichenoid dermatitis in which symptoms similar to the above appeared but in which the causative mechanism was probably atrophy and destruction of the sweat ducts. This is only a preliminary paper; the mechanism and significance of the "sweat retention syndrome" constitute a field for research.

H. R. Vickers.

INDUSTRIAL OPHTHALMOLOGY

Selenium Burn of the Eye. Report of a Case, with Review of the Literature MIDDLETON, I. M. (1947). *Arch. Ophthal., Chicago*, **38**, 806.

Selenium and its compounds are used in the manufacture of ruby glass and stainless steel and in a wide range of industrial processes. They have been the cause of many cutaneous burns as well as of acute and chronic types of general intoxication; but no case in a human being of selenium burn of the eye has hitherto been published. Most of the selenium compounds are vesicants, producing lesions comparable to severe and intractable acid burns. The patient, a chemist aged 36, was accidentally sprayed with selenium dioxide, sustaining burns of both eyes. When examined an hour after the accident he had severe burning pain, lacrimation, and extreme blepharospasm. Palpebral and bulbar conjunctivæ were intensely injected. There were first-degree burns of the face and eyelids. Six hours later there was marbling of the lower half of the bulbar conjunctiva with fluorescein staining of this and the lower part of the cornea. Sixteen hours later signs and symptoms were more pronounced and vision was blurred. A mucous membrane graft was applied to the lower half of the right eye. This eye recovered more promptly than the left, but the graft led to postoperative ectropion and partial symblepharon. Complete recovery from the acute symptoms occurred in 10 days.

A. J. Ballantyne.

Corneal and Conjunctival Pigmentation among Workers engaged in Manufacture of Hydroquinone. ANDERSON, B. (1947). *Arch. Ophthal., Chicago*, **38**, 812.

The author presents a study of a large group of workers in whom more or less pronounced pathological changes in conjunctiva and cornea are due to exposure to quinone or hydroquinone. The lesions are confined to the interpalpebral zone and vary in severity according to the duration of exposure to the deleterious substance. After about 2 years' exposure a brownish stain appears in the interpalpebral portion of the conjunctiva. The affected surface has a dry appearance and is covered with a white foamy deposit. After another period of 2 to 3 years the conjunctiva becomes thicker and drier; small discrete dark brown granules or globules are observed in the deeper structures. Pigment migrates into the arcus zone of the cornea. After a further period of 5 or more years there is an increase in the size and number and spread of the granules and the extent of the staining. In time the conjunctival staining fades, but there is permanent damage to the cornea with opacity, increase in astigmatism, and possibly keratoconus. Microscopical examination of the corneal lesion confirmed the results of slit-lamp examination, intercellular free granules and intracellular globules being found in the epithelium and in the anterior layers of the cornea. The clinical appearances resemble those seen in ochronosis.

It is suggested that the absorption of the chemical material is a local tissue reaction to a chemical, which is both water-soluble and fat-soluble, in an alkaline medium (tears) aided by the blinking movements of the lids. The author assumes that the hydroquinone or some modification of it dissolves in an alkaline aqueous medium (tears) and, being fat-soluble, is also combined in the cornea and conjunctiva by some interaction with fat in the corneal reservoirs and with the fat present as a result of injury to the cornea. This "bound" material in the interpalpebral fissure, being exposed both to light and to the specific effect of the intracellular oxidase acting in the presence of radiant energy, undergoes modification, as do the intermediate products of hydrocarbon metabolism in ochronosis; a melanin-like material is deposited in the fat reservoirs. The author points out that, although some patients have improved on removal from exposure to the irritant, others have developed corneal dystrophy, dyskeratosis, and possibly keratoconus, as well as appearances suggestive of Bowen's disease. A cautious attitude seems called for.

A. J. Ballantyne.

ENVIRONMENT

Effectiveness of Ultraviolet Irradiation of Underground Workers. (In Russian.) GORKIN, Z. D., STANISLAVSKI, Y. M., and GOVORCHUK, R. Y. (1948). *Gigiena*, **3**, 29.

The effect on health of untra-violet light was studied in a group of 122 underground workers. Some authorities consider the increase in hæmoglobin value and erythrocytes with altitude to be due principally to the increased amount of ultra-violet light. Objectively and subjectively the workers exposed to it improved in tone, working capacity, and general well-being. There was a tendency to a rise in hæmoglobin value, with some increase in lymphocytes and monocytes. It is concluded that underground workers benefit from this treatment.

G. C. Pether.

Bacterial Contamination of the Air in Living Quarters with Various Densities of Population. (In Russian.) EPSTEIN, F. S., and SALAMANDRA, E. G. (1948). *Gigiena*, **3**, 14.

Experiments were made to determine the aerial content of streptococci and the variations occurring with increase and decrease of living space per person, the season of the year, and other factors. When each person occupied from 2·5 to 3·6 sq. metres 468 colonies were counted on a medium, whereas when living space increased to from 10 to 18 sq. metres the number of culture colonies fell to 86. Two seasonal rises were observed, one in about April and the other in about October. These would coincide in Russia with a fairly rapid change in temperature and living conditions. When accommodation had improved, so that each person had his own room, there was a fairly sudden fall in the colony counts. It is thought that the figures obtained justify further work

on the value of aerosols, particularly since the bacterial counts rose considerably when any illness of the nose and throat or respiratory tract affected the persons under observation. *G. C. Pether.*

Principles of Standardization of an Artificial "Microclimate." (In Russian.) SHAKHBAZYAN, G. K., and VITTE, N. K. (1948). *Gigiena*, 3, 22.

The heat balance was maintained during light work with an external temperature of 25° C., but for heavy work 10° C. was ideal, and for extremely heavy work the freezing point. A "climate" undergoes variations under many headings, and that physical output decreases with rising temperature, at least above a certain point. Corresponding with the rise in temperature is an increase in pulse rate and greater fatigue with less efficiency of the heart. [The article is a review of factors already well known.] *G. C. Pether.*

Factors Affecting Warmth, Comfort and Stuffiness in Domestic Rooms. YARNOLD, K. W. (1947). *J. Hyg., Camb.*, 45, 434.

This investigation was to ascertain: (*a*) whether standards accepted for large, evenly-heated rooms apply to small "domestic" rooms, and, if not, what new standards were necessary; (*b*) the optimum contributions, as regards warmth comfort, of air heating and radiation to total warmth; (*c*) the physical conditions responsible for sensations of freshness and stuffiness.

Thirteen subjects entered a room heated only by convection to an "equivalent temperature" of 62°±1° F. with an outside temperature of 45° to 50° F.; they recorded their sensations as "comfortable" (9), "confortably cool" (3), and "slightly too cool" (1). In rooms heated by fires to the same equivalent temperatures in their centres, the same 13 subjects complained of cold backs, and, if allowed to choose the most comfortable position in the room, sat near the fire. It was evident that the [commonly accepted] standard of 60° to 65° F. was inadequate for rooms heated by unilateral radiation, or that the instruments used were unsuitable for such rooms, or both.

Panels of 28 to 33 subjects, one at a time, entered a large room equipped with adjustable controlled air heating and a gas fire at one end. Even when the air temperature is high enough (above 65° F.) to ensure adequate warmth without extra radiation the subject still appears to desire radiant heat. "When the temperature conditions operating on the back are too low for comfort, the subject attempts to compensate . . . by overheating the front of his body." Observations suggested that "where a large proportion of heat radiation is unidirectional the sides of the subject facing towards and away from the source of heat must be treated separately, and that the cooler side must be exposed to an equivalent temperature not much less than 65° F." The desirability of measuring separately, in domestic rooms, the conditions to which the sides of the body proximal to and remote from the fire are exposed led to the design of double eupatheoscopes and double globe thermometers. From tests by 8 subjects in their own homes with double globe thermometers it is concluded that the presence of unilateral radiation does not reduce the need to heat the side of the body away from the fire, a need which is best catered for by "radiators" or air-conditioning plants maintaining consistently an equivalent temperature of 60 to 65° F. Over and above this essential need, the average subject appears to desire radiation to the extent of about 70 British thermal units per sq. ft. per hour. Experiments suggested that the compensation of a warm front surface for a cold back is psychological rather than physiological.

To ascertain the relation of freshness to warmth a large room was equipped with a gas fire at each end and with separate means of air heating controlled by a thermostat. An electric fan was used to modify the rate of air movement. Subjects were asked to choose the most comfortable position as regards warmth and then to record their sensation of freshness or stuffiness as "extremely fresh," very fresh, fresh, neutral, slightly stuffy, stuffy very stuffy. Measurements were also made of the rate of air movement. A clear relation existed between air temperature and freshness when subjects were suitably warmed. Neutral freshness was perceived at about 61·5° F. An increase of 5° F. was sufficient to make conditions slightly stuffy.

The effects of radiation on freshness and stuffiness were studied by asking subjects to take up what they considered to be the most comfortable position in front of a fire specially made up and connected to thermocouples so that its surface temperature could be measured continuously and kept constant. At the position chosen the air temperature was measured, and the subject was asked to record his sensation of stuffiness or freshness on the scale already given. It was possible to plot a curve showing the effect of air temperature on freshness, and from this curve to determine an air temperature which would have raised or lowered the subject's sensation of stuffiness to the neutral position. For any particular surface temperature of the fire the mean of these "neutral" temperatures was plotted against the peak wave-length of the radiation. In this graph an air temperature of 61° F. indicated that the wave-length has a neutral effect as regards freshness. An air temperature higher than this indicates that the wave-length concerned has a specific "freshening" effect, because the air temperature could be permitted to rise to 64° F. in the presence of this radiation without pushing the sensation of stuffiness beyond the neutral point. Temperatures below 61° F. indicated that the wave-length concerned causes stuffiness. The graph also shows that certain wave-lengths (2, 3·5, and 4·5 μ), known not to be absorbed by the skin, induce sensations of freshness whereas others (3, 4·1, and 4·7 μ) cause stuffiness. Peaks at 3, 4·1 and 4·7 μ should therefore be avoided in the design of gas and electric fires.

J. Greenwood Wilson.

GENERAL

Clinical Investigations and Considerations on the Influence of the War Years on Pregnancy. II. Influence on Toxæmias of Pregnancy: Albuminuria. III. Influence on Sympathetic Disturbances. IV. Influence on Abortions and Premature Deliveries. (Indagini cliniche e considerazioni circa l'influenza del periodo bellico sullo stato puerperale. II. Influenza sulle tossicosi gravidiche: Albuminuria. III. Influenza sui fenomeni simpatici. IV. Influenza sugli aborti e sui parti prematuri). CANNA, S. (1947). *Ginecologia, Torino*, 13, 430, 497, 515.

The effects of living conditions and occupation on pregnancy were investigated between 1933 and 1945 in Novara.

There was a decrease in toxic manifestations during the war. The percentage was slightly lower for multiparæ than for primiparæ. The decrease was more noticeable among women living in the country and

among land workers. It is the author's opinion that the nutritional factor is important in this decline in incidence of toxæmia. Carbohydrates, vegetables, and fruit figured prominently in the diet of pregnant women in the province of Novara, while animal protein and lipids were less than in peacetime.

The number of cases without sympathetic disturbances increased progressively between 1933 and 1945, with a minimum of 16·2% in 1934 and a maximum of 40·5% in 1945, and the number in which sympathetic disturbances were very accentuated decreased progressively during the same period, with a maximum of 30% in 1935 and a minimum of 5·1% in 1945. For primiparæ without sympathetic disturbances the figures were 29·7 % before the war and 35·4% in wartime; for multiparæ they were 23·7% and 36·2%. The decrease in incidence of pronounced sympathetic disturbances was greater in multiparæ. There were no great differences in this respect between urban and rural dwellers. The decrease in incidence of accentuated sympathetic disturbances was most evident in housewives (from 25·7% before the war to 7·1% during the war). Many authors have suggested that the cause of sympathetic disturbances in pregnancy is hyperexcitability of the nervous system. If this were the case the war should have brought about an increase in such phenomena. Endocrine and ovarian factors are also unrelated to the observed fall in incidence of sympathetic disturbances. It is thought that diet played an important part.

The incidence of abortion and premature delivery was studied at the Obstetric School of Novara between 1933 and 1945. Before the war the incidence of abortion in 4,523 pregnant women was 12·2%; during the war it was 15·4% in 4,113 cases. The figures for primiparæ were 6·7% and 9%; for multiparæ they were 16·5% and 20·6% respectively. For women living in towns the incidence was 10·8% in peacetime and 12·8% in wartime; for those living in the country the figures were 13·7% and 17·6%. The incidence in housewives was 11·7% in peacetime and 14·5% in wartime; in factory workers 12·1% and 14·2%; in land workers 14·4% and 21·4%. During the war there was a general slight increase in the incidence of abortion in both primiparæ and multiparæ. The increase was more pronounced in land workers. The incidence of premature delivery was 13·8% in peacetime and 21·4% in wartime. This increase was more accentuated in women living in towns and in factory workers.

The author does not consider that abnormal condition of the genital organs or of the ovum, or dysfunction of the endocrine gland caused the increase in abortion and premature delivery. The incidence of acute infectious diseases did not increase during the war, but syphilis was more prevalent. According to Roberto, emotional shock is not a cause of abortion or premature delivery. The author believes that the deficiency of fat-soluble vitamins in the diet during the war was a cause of increased interruption of pregnancy.

Rina Saunders.

The Social and Economic Significance of Thrombo-embolism. (Trombo-embolisjukdomens sociala och ekonomiska betydelse.) ZILLIACUS, H. (1948). *Nord. Med.*, **37**, 624.

This article stresses the clinical, social, and economic after-effects of acute thrombosis of the deep veins of the leg. These chronic changes to a large extent develop after the acute stage has passed off; active treatment in the acute stage is a means of preventing them. An analysis was made of 680 cases treated by conservative methods from 6 to 14 years previously. The average age at the time of follow-up study was 50. No case that had been treated actively by heparin or dicoumarol was included, nor any case of direct injury to the legs. Clinically only 48 or 6% of the patients had completely normal legs, and symptoms or signs varying from pain and heaviness to œdema and eczema were found in 90% of the cases. Ulceration was persistent or recurrent in 136 cases. Socially and economically, it is difficult to assess the disability accurately, but an indication of this is given by comparing the lengths of stay in hospital with and without active treatment and by a series of estimations of financial loss to the patient resulting from lengthy disability. As a direct sequel of thrombosis 54 patients were unfit for further work, 81 had to change their work, and 127 had to have permanent extra help in the house. *J. W. S. Lindahl.*

The Quaternary Ammonium Compounds in Sanitization. MCCULLOCH, E. C., HAUGE, S., and MIGAKI, H. (1948). *Amer. J. publ. Hlth.*, **38**, 493.

Some Factors Affecting the Properties of Quaternary Ammonium Compounds as Sanitizers. RIDENOUR, G. M., and ARMBRUSTER, E. H. (1948). *Amer. J. publ. Hlth.*, **38**, 504.

More than 1,000 of these compounds have been produced. The School of Public Health of the University of Michigan is investigating their action, including: (1) relative efficiency; (2) effect of organic matter, temperatures, hydrogen-ion concentration, and character of water; (3) relative resistance of different organisms; and (4) chemical methods of testing cationic concentration. Certain of these compounds have marked disinfecting properties but there is wide variation in their effective actions. Their efficiency is affected by temperature, hydrogen-ion concentration, organic matter, and the presence of calcium and magnesium in the water. Their bactericidal action was tested against such human pathogens and non-pathogens as *Salmonella typhi*, *Shigella dysenteriæ*, *Salmonella schottmülleri*, *Staphylococcus aureus*, and types of *Bacterium coli*. In general all these organisms showed the same susceptibility, while such organisms as *Pseudomonas pyocyanea* and *Serratia marcescens* (*Bacillus prodigiosus*) were relatively much more resistant. Chemical methods are available for measuring the actual concentration of any of the substances, but this type of estimation is of limited value, as it does not assess the bactericidal value of a particular solution. The data so far accumulated indicate that these quaternary compounds are of value for disinfecting food utensils and dishes, but they must be employed in an intelligent manner and with knowledge of the limitations and range of action. They do not afford such positive protection as the hypochlorites, and they are inferior to hot water or steam. It is urged that the U.S. Public Health Service should continue its study on these products. Each package should state the chemical composition of the material, otherwise there would be no guarantee of the efficiency and suitability of the substance.

The Control of Phlebotomus in Peru with DDT. HERTIG, M., and FAIRCHILD, G. B. (1948). *Amer. J. trop. Med.*, **28**, 207.

"Experiments to test the possibility of area-control of *Phlebotomus* with residual DDT were carried out in Peru, 1945 to 1947. The results furnish additional sup-

port for the effectiveness of house spraying in protecting persons indoors. Treatment of stone walls (the principal outdoor shelters and breeding places) produced marked reduction of sandflies. Treatment of stone walls combined with house spraying reduced sandflies to an extremely low level. This effect still persisted after 12 to 19 months. The results were sharply localized within the sprayed areas, sandflies occurring in normal abundance in houses or caves 75 to 200 yards (68·6 to 183 m.) distant. Practical control programmes in camps of two large construction projects gave an extremely high degree of sandfly control, followed by virtual cessation of new cases of cutaneous leishmaniasis or bartonellosis. Analysis of the results in terms of the habits and life-history of *Phlebotomus* supports the possibility of achieving practical control by methods applicable to many of the *Phlebotomus* regions of the world. Their flight habits make sandflies vulnerable to residual DDT throughout their adult life. The long life-cycle delays the recovery of a depleted sandfly population."

Recent Mosquito Eradication Campaigns. BUSVINE, J. R. (1948). *Nature, Lond.*, **161**, 189.

The author recounts the history of four eradication campaigns. Two, one in Brazil and the other in Upper Egypt, were directed against a single species of malaria vector, *Anopheles gambiæ*, which does not normally inhabit these regions. Both these campaigns have now been brought to a successful conclusion, and it is believed that the vector can be prevented from re-entering the region by the efforts of a small sanitary guard, which could be maintained at a relatively trivial cost.

Statistics of Anopheline Eradication Projects

Zone	Anopheline Species	Area Involved	Men Employed	Total Time	Cost* £1,000's
Brazil ..	*gambiæ*		2,000	3½ yrs.	530
Upper Egypt..	*gambiæ*	4,100 sq. km. 1,500 sq. mls.	4,000	2 „	800
Cyprus	*superpictus*	9,300 sq. km.	100	3 „	15 (7 months)
	sacharovi	3,600 sq. mls.			
Sardinia	*labranchæ*	23,000 sq. km. 9,000 sq. mls.	6,000†	3† „	more than 500† a year

* On the basis £1 = 4 dollars = 2,000 lira.
† Estimates.

The remaining two campaigns, one in Cyprus and the other in Sardinia, are directed against mosquitoes indigenous in these centres and are not yet complete. They are progressing well, but they demand " all the faith and energy, as well as the technical and administrative skill, which are being devoted to them."

R. M. Gordon.

The Importance of Coverage in DDT Residual House Spraying for Control of Anopheles quadrimaculatus Mosquitoes. MCCAULEY, R. H., FAY, R. W., and SIMMONS, S. W. (1948). *Publ. Hlth Rep., Wash.*, **63**, 401.

" Tests made by releasing *Anopheles quadrimaculatus* mosquitoes in rooms in which varying amounts of surface were treated with a residue of DDT at 200 mg. per square foot indicated that (1) satisfactory control of this mosquito cannot be expected from a spot treatment in which only the predictable resting places in a room are sprayed ; (2) coverage of the predictable resting places plus the walls and ceilings in a room is a more effective method of application than that in which only the walls and ceilings are sprayed ; (3) the amount of total area covered with DDT not only affects the initial knock-down efficiency of the treatment of the room, but the residual quality as well ; (4) based on the criterion of a 4-hour knock-down, complete treatment is experimentally more effective than the regular treatment ; (5) efficient application is necessary for the greatest residual effect of DDT spray."

[This paper contains valuable information which does not lend itself to condensation, and it should be consulted in the original.] *R. M. Gordon.*

Field Tests with Tick Repellents. BRENNAN, J. M. (1948). *Publ. Hlth. Rep., Wash.*, **63**, 339.

The author in a previous paper showed that, out of 15 chemicals tested, a mixture of phenyl*cyclo*hexanol and butylacetanilide was most promising as a protection against *Amblyomma americanum* and *Dermacentor andersoni*. The present paper describes the results of tests of these drugs carried out with human volunteers at a military camp in an area densely infested with the lone star tick, *A. americanum*. Men wearing treated and untreated uniforms were exposed to tick infection for about 4 hours a day, the ticks being removed and counted hourly. The results obtained showed that under the conditions of employment butylacetanilide was an excellent repellent of nymphs and adults (larvæ were not present in sufficient numbers to be significant) of *A. americanum* for 10 days, and was superior to all other drugs tested. Incidental observation suggests that clothing impregnated with butylacetanilide gives complete protection against *Trombicula*. " No data are available on its toxicity, but related compounds have been pronounced safe, and in tests described here on 29 persons no objectionable reactions were found."

R. M. Gordon.

Toxicity of γ-Benzene Hexachloride in Clothing. HORTON, R. G., KAREL, L., and CHADWICK, L. E. (1948). *Science*, **107**, 246.

Animals exposed to an acetone solution of the pure γ isomer of hexachlorocyclohexane and mixtures of hexachlorocyclohexanes containing 83% of γ isomer, or fitted with suits of herringbone twill impregnated with an acetone solution of hexachlorocyclohexane (83% γ isomer) of such strength as to yield a concentration of 2 g. of γ isomer per square foot of cloth, developed symptoms of hexachlorocyclohexane intoxication and a number died within a week of exposure. Rabbits and rats were more sensitive than guinea-pigs. Care was taken to eliminate ingestion and inhalation of the compound. Movement appeared to increase the hazard. Previous tests at Orlando, Florida, had shown that this concentration for impregnation of twill was highly effective against mites. The authors conclude that such a concentration is sufficiently hazardous to some mammals to warrant the utmost caution in the use of γ isomer in a concentration of 2 g. as a miticide for impregnating human clothing. *G. R. Cameron.*

Pathological Changes in Welders. (La patologia dei saldatori.) PECORA, L. (1948). *Folia med., Napoli*, **31**, 150.

After reviewing the types of exposure in 78 welders mainly on naval work, the author concludes from a general clinical study that there is no specific occupational syndrome. *John Hambling.*

Action of DDT and a-Hexachlorocytohexane on Ticks and Moths. (Über die Wirkung von 4,4¹-Dichlordiphenyl-trichlormethylmethan und von γ-Hexachlorcyclohexan auf Zecken und Schaben.) LANGBEIN, G. (1948). *Z. Hyg. InfektKr.*, **127**, 570.

DDT in concentrations of 0·01 to 1% acts more quickly at high temperatures against ticks (*Ornithodorus moubata*) and moths (*Phyllodromia germinaca*). An increase of 15° (from 18° to 35° C.) increase its insecticidal action two- to threefold. γ-Hexachlorcyclohexane in a concentration of 0·01% had a similar effect, and its insecticidal action was greater than that of DDT. Ticks (nymphs) and moths (larvæ and adults) could be exposed without any harm to the normal vapour pressure of DDT for 3 weeks, thus revealing some resistance. γ-Hexachlorcyclohexane is effective against *Pediculus capitis*, and was found to be very effective against head lice at a concentration of 1% when used on patients. About 8 g. of the powder is rubbed thoroughly into the hair and skin, and the head is covered with a cap which is left overnight. After 10 hours the hair is combed and washed : even after 3 hours the irritation disappears.

R. Wien.

Mist Control with Addition Agents in Chrome Plating. SILVERMAN, L., and THOMSON, R. M. (1948). *J. industr. Hyg.*, **30**, 303.

In addition to exhaust ventilation, several methods have been proposed for the reduction of plating-bath mist and spray. A new commercial agent, named "no-cro-mist," for controlling chromium plating has been investigated by the authors. Measurements with a standard acid plating solution showed that the agent lowered its surface tension from 64 to 26 dynes per cm. Performance tests were made with a model plating-bath consisting of a glass jar of 3½ litres capacity. Lead electrodes (0·1 sq. ft. : 0·009 sq m. in area) were placed in the bath, with current densities of 150 to 200 amperes per sq. ft. of plating surface. Ventilation was provided by a canopy hood reaching within 5 cm. of the bath edges. Exhaust ventilation gave an annular velocity between bath and canopy of 250 feet per minute. The apparatus was tested for 45 minutes without the addition of the agent, followed by a 5-hour period with it. The agent at first prevented almost all the evolution of mist, the concentration of mist in the exhaust duct being reduced from 0·6 mg. per 10 cu. m. to 0·0043 mg. At the end of the 5 hours it was still less than half the control value.

H. M. Vernon.

Studies on Q Fever : Complement-fixing Antibodies in Meat Packers at Fort Worth, Texas. STRAUSS, E., and SULKIN, S. E. (1948). *Proc. Soc. exp. Biol., N.Y.*, **67**, 139.

Since *Rickettsia burneti* was demonstrated as the cause of an outbreak of Q fever and recovered from ticks in Texas, the authors have carried out an examination for complement-fixing antibodies to *R. burneti* on samples of serum, sent for routine syphilis tests, from employees of meat-packing plants. There was no clear evidence associating positive reactors with any particular form of employment, while positive tests for syphilis were obtained in 39 (2·7%) of all the samples, and in 4 (3·5%) of the 114 sera containing demonstrable rickettsial antibodies ; this would indicate no significant relation between the two antibodies. Existing evidence suggests that the complement-fixation test with yolk-sac antigens of *R. burneti* is specific for Q fever. A rise in titre has been found in proven cases, and no cross-reactions with other rickettsial diseases have been found. Control tests on a number of positive anti-rickettsial sera showed that non-specific fixation by an antigen prepared from uninoculated normal yolk-sacs did not occur. The significance of the results obtained is discussed. They are believed to indicate the existence of unrecognized exposure to *R. burneti*.

G. T. L. Archer.

PROCEEDINGS OF THE ASSOCIATION OF INDUSTRIAL MEDICAL OFFICERS

FIFTY-SECOND MEETING

The Fifty-Second Meeting of the Association was held in Glasgow from June 15 to 18, 1948. This annual provincial meeting was held at the invitation of the Scottish Group and was a success both in the merit of the scientific papers read and socially. The President, Dr. A. J. Amor, was in the Chair, and eighty-five members attended the various sessions.

At the opening session on June 15, Prof T. Ferguson, Professor of Public Health at Glasgow University, read the paper entitled "Early Scottish Essays in Industrial Health," which appeared at p. 180 of the October, 1948, issue of the *British Journal of Industrial Medicine*.

Members then visited the University buildings and were conducted to the Hunterian Museum, and other parts of historical and architectural interest, and, by invitation of the Principal and Vice-Chancellor, Sir Hector Hetherington, were entertained to lunch in the University. In the afternoon visits were paid to the following industrial establishments: (1) Port Medical Services (during this visit the Medical Services for the Clyde, as developed by the Clyde Trust, were seen); visits were also paid to the shipbuilding yard of Messrs. John Brown, and the shipbreaking yard of Messrs. Arnot Young at Clydebank; (2) Rolls Royce Factory, Hillington, at which Dr. Collier demonstrated photographs of cases of oil acne and chrome ulceration, and arranged for a tour of the factory; (3) Haven Products, where Prof. Ferguson showed the attempt that had been made to employ seriously disabled persons.

On June 16, seventy members and friends sailed down the Clyde to the Kyles of Bute. During the morning, Dr. J. D. P. Graham, I.C.I., Fellow attached to the Department of Pharmacology, Glasgow University, read a paper on hydrazoic acid. Dr. Graham said that hydrazoic acid, which was also known as azoimide, was a pungent explosive gas discovered by Curtis in 1890. Some of its biological properties were investigated by Smith and Wolf in 1904. Recently Dr. Graham had himself re-investigated the actions of the neutral, stable water-soluble sodium salt of azoimide. This substance stimulated the central nervous system of animals and might cause death in violent convulsions, as did hydrazoic acid. Respiration was violently stimulated, there was a profound fall in blood pressure from a direct action on the blood vessels, and the heart was greatly stimulated. The motor activity of the bladder and gut was increased, with consequent evacuation, but the uterus was less sensitive. The coronary arteries were relaxed, and the bronchi were dilated by azide. Hydrazoic acid differed from azide in its actions in that it was more powerful and, being a corrosive substance, it produced pulmonary œdema and exudative pulmonitis after a preliminary bronchial spasm. Dr. Graham said that cases of acute irritative reactions in the conjunctivæ and mucous membranes and collapse from hypotension had occurred as a result of deliberate or accidental inhalation of excessive concentrations of the gas, but no ill effects resulted in workmen exposed intermittently to lesser concentrations of azoimide fume over a period of many years. During inhalation the systolic and diastolic pressure of ten men investigated fell to very low levels, but recovered subsequently. There was accompanying headache, palpitation, and some dizziness. No evidence of blood dyscrasia, liver or kidney damage, or indeed any impairment of health attributable to the inhalation of azide gas was detected. Nevertheless such a powerful substance had to be regarded as a toxic hazard worthy of careful investigation and control in any industrial process where azide was used. The possibility of release of hydrazoic acid fumes at any stage of the process had to be kept in mind, and measures suggested for the removal of this potent agent which had marked hypotensive properties in a concentration of one part per million or less.

Mr. J. Scott Tough, a member of the staff of the Burns Unit, Glasgow Royal Infirmary, followed with an interesting paper on some aspects of skin loss. He showed photographs of injuries treated by skin grafting.

On June 17, Prof. Philip I. Dee, Professor of Natural Philosophy, Glasgow University, read a paper on radioactivity, in which he described in a clear and interesting manner the physical properties of radiations. Mr. A. A. Charteris, Director of the Radiotherapy Department, Western Infirmary, Glasgow, read a paper on some biological implications of radiology in industry. Mr. Charteris said that biological effects resulting from exposure to radiations were caused by their absorption in the tissues, in the process of which they parted with some of their energy with certain secondary effects. The general rule was that the most easily affected tissues were those in a state of physiological activity; it was the nucleus in mitosis which was most readily affected. Thus, in ordinary clinical radiotherapy, it was such tissues as the skin, the sites of hæmopoieses, and the gonads which had to be specially considered. This selective action was the basis of clinical radiotherapy, and one of the reasons why certain tumours could be treated without damage to normal tissue, the mechanism probably acted through effects upon intra-cellular enzymes and upon the chromosomes themselves. Modern knowledge of how the higher dose levels should be attained with due regard to the physical factors modifying their effect upon the body had largely eliminated the bad after-effects which were associated with the earlier stages of radiotherapy. Protection from ill-effects of irradiation in industry was bound up with prevention of the cumulative effect of many sub-lethal doses. Since such doses produce no immediate reactions, and their ultimate effect may not be known for a long time, such exposure, if permitted, may be much more dangerous and subtle in effect than larger ones. Mr. Charteris went on to consider the sources

of irradiation which might be met with in industrial concerns. The first of these comprised radio-active substances which might exert an effect either by the deposition of active deposits upon the skin, or by the actual ingestion of radio-active materials. The second way in which the body might be affected was by external radiation, either from an *x*-ray plant, or from a filtered radium source, in which case gamma rays would be concerned. It had long been known that the blood showed certain changes after undue irradiation of the body. First there was usually a change in the white blood corpuscles, and it had long been thought that the typical reaction was a fall in the total count associated with relative lymphocytosis. In recent years it had been shown that this picture could be due to other causes than irradiation, but it was one which should be watched for. Anæmia was a result not usually seen in clinical work, but it was described by writers on industrial subjects. It was said that the aplastic form tended to follow large doses of external radiation, while the megaloblastic type was more frequently seen after alpha rays had been able to take effect, as when radio-active material had been absorbed.

Exposure of the gonads was also described. As everyone knew, the achievement of certain dose levels led to cessation of physiological activity except in the interstitial cells, and to sterilization. What was less well understood was the possible effects of much smaller doses than this, especially if they were applied over a long period. Low-dose irradiation of the ovaries was regularly carried out in the United States as a therapeutic measure for various ovarian disorders, including sterility, and it was claimed that there could be no ill effects either to women so treated or to any offspring. Animal experiments had shown certain genetic effects, though these were generally after larger doses than those deliberately applied clinically, or encountered accidentally in industry. So far, no definite genetic effects had been discovered in man, but the mutations concerned were generally thought to be recessive and so it might be a very long time before they became obvious.

These agents might also affect the human skin. There might be chronic dermatitis with atrophy of the skin, including its glands, and interference with nail growth. Later might come chronic fissures, and susceptibility to local sepsis, together with the formation of warty growths and even squamous carcinoma. In the consideration of protective measures for those who might be working with radiations, a " tolerance dose " had been suggested. This was defined as the dose which a person could receive indefinitely without any biological effect, and the accepted limit was now 0·5 r per week. It should be observed that this was a body dose, and could not be applied to finger exposure. The two chief methods in vogue were the ionometric, in which a charged condensor was employed, and the photographic, where ordinary film was used and subjected to standard development so that the tint might be compared with various standards. Mr. Charteris said that so far as radio-active substances were concerned we had to deal with radon apparatus, the handling of radio-active isotopes, the working of an atomic energy pile, and luminizing as widely applied in industry. The first two of these were largely medical in their application, and much of what had to be considered was contained in the regulations for luminizing. Workers had to be protected against contamination of the skin, ingestion of material, and inhalation of radon. The stock of radio-active material was protected behind lead of sufficient thickness to obviate any gamma ray effect, and as small quantities as possible were exposed at any one time, the distance effect being made use of. The workshop had to have an impervious floor and suitable protected work benches provided at which an extraction ventilation system was in operation. Any dry powder was worked with in a screened cabinet, and there were various ingenious devices by which paint could be applied with a minimum of risk of contaminating the fingers. Employees had to be given full facilities for washing, and they carried some form of dose recorder such as photographic films, and had regular medical examinations. The luminizing paint used nowadays contained much less radium than was used during the war, the amount being 12 microgrammes per gramme of paint. External radiation was generally employed in the examination of castings and welds for faults which would not otherwise be obvious. Filtered sources of radium were used at one time for this, but were now hardly ever employed since sufficiently penetrative *x* rays were readily available and were much more easily controllable. Qualities of *x* rays at present employed were commonly those associated with the electrical potentials of 220–400 K V. and in these cases the protective problem was simple. Those operating the set retired to a protected control cabin at the time when the exposure is being made, and precautions were taken so that other workers were neither in the direct path of the beam nor sufficiently near to obtain any significant dose through the phenomenon of the " scattering " of the rays. Where more penetrating *x* rays were used, such as 1,000 or even 2,000 K V., much more elaborate arrangements were necessary. The lecture was illustrated by lantern slides. In the afternoon, visits were paid to the Atomic Energy plant at Glasgow University, which was demonstrated by Prof. Dee, and to the Erskine Hospital where seriously disabled ex-service men and civilians were employed.

In the evening a dinner was held at which seventy-four members and five guests were present. The toast of the Association was proposed by Mr. W. Hope Collins, Director of William Collins Sons and Company, Publishers, Glasgow. In an encouraging address Mr. Collins gave his views on the practical application of occupational health to the needs of industry. For the past eight years he had tried to build up in his business a structure which had, as one of its main pillars, occupational health. The first great principle which had to be accepted today by everyone was that both sections of industry—capital and labour—could never, alone in control, be successful, either happily or otherwise. A start had to be made therefore, with joint goodwill. Mr. Collins went on to describe the present accepted task of a medical officer of a large or medium-sized works, as follows : (1) to organize the surgery so that he can deal with injuries and alleviation of minor ailments ; (2) to advise on matters dealing with safety, heating, lighting, etc. ; (3) to examine new workers ; (4) to maintain a close link with the personnel department. Although this did not sound much, it often took a long time to achieve. It was his experience that management and employees were at first equally ignorant and at times suspicious—the management fearful lest their authority was challenged and discipline weakened, the employees that something was being imposed upon them. Both were natural fears ; therefore before any cut-and-dried schemes were started it was essential to begin with joint consultation between employees and management. This could quite easily be started with a " health or safety joint committee," perhaps with the setting up at the same time of a surgery under the charge of a Sister. This Committee would become the open

forum where grievances could be aired and cleared. Later constructive suggestions could be put forward and at this stage an industrial medical officer could be introduced. He could carry the scheme a step further by bringing his specialized knowledge to bear on such questions as lighting and safety.

A chiropodist was a necessary and valuable addition to an industrial surgery in industries where workers were on their feet; and there might also be a dentist. Examination of new workers could be quite separate and more complete than any examination by Factory Act doctors. While all this was going on, the medical officer studied the particular requirements of the firm in question, the type of work, the type of labour, etc. No set scheme could be laid down for all works, even within the same industry.

Any further progress now depended entirely upon the medical officer himself. From the time he entered the works he should be scrupulously fair to both management and employees. He would thus earn the respect and trust of both, and particularly of the employees, for it was their welfare that was of paramount importance. If he gained this trust the benefits to industry and social life generally were immense. The medical officer's activities would also cover two main fields, vocational guidance and industrial relationships. Under the first, the doctor considered the physical and mental characteristics of each worker. These were then matched with the requirements of the operations required. In this way, errors in first placing of young workers were eliminated. Nothing was more soul-destroying for a young man or woman than to find himself in a job to which he was not adapted or in which he was not really interested, at a time when it was too late to make a change with any certainty of success. The medical officer could also therefore be of invaluable assistance in the planning of apprentice training schemes.

With regard to industrial relationships, Mr. Collins said that the Medical Officer could create that industrial morale which was of equal importance with military morale. By constant education of both management and employee in such things as hazardous processes, health, hygiene, diet, clothing, he could help to keep people both mentally and physically fit. The effect within the works would be immediately noticeable. From the very fact that he approached every problem from an unbiased angle, he would be listened to with confidence by both sides. It was the continual application of this unbiased attitude that would gradually change what in industry was called "sides" and "meeting round the table."

The toast of the Guests was proposed by Prof. F. A. E. Crew, Professor of Public Health and Social Medicine at Edinburgh University. After paying tribute to the guests individually, Prof. Crew referred to the role of the Universities in relation to industry. The opinion that staffs of university departments and those who emerged therefrom were men whose feet were high off the earth and whose heads were in the clouds was still far too prevalent and there was still far too much misunderstanding between what was called the working man, who earned his living doing something he did not wish to do, and the "non-working man," whose creative or productive efforts gave to him great emotional satisfaction. The fundamental problem that now faced industry was not one that could be defined as re-equipment, redeployment, or modernization in respect of machinery or method but rather the attitudes of mind which were now called the "stress diseases." Men and women worked because they were forced to work in order to escape the results of not working—work or want was the admonition encountered on all sides. Some men and women worked out of a most praiseworthy sense of social duty and apparently enjoyed a sense of duty fulfilled. Even fewer men and women were encouraged by society to indulge in self-exploration and to seek self-discovery in advancing the boundaries of natural knowledge or in adding to the sum total of beauty in this world. To them the reward of work, if this be work, was the satisfaction to be found in performance. It was most unfortunate that in our social evolution we had so allowed things to arrange themselves that most kinds of energy expenditure of value to the community had no kind of emotional appeal, for it was the emotional rather than the physical or intellectual elements in man's nature that yielded the greatest satisfaction. The majority of people were obliged by circumstances to turn away from work to find their satisfaction in amusement, and it could not be denied that many of the activities within society which did not make for human betterment were in their ultimate nature the expression of cravings for change or for pleasure as a reaction to the monotony of daily work. Industrial medical officers were heavily engaged in securing an ever-increasing control over dangerous trades. Today those trades were most dangerous which were the most drab and the most dull. In spite of all the difficulties which stood in the way it seemed that the aim of society, fashioned by the guidance of medicine, should be the provision for every individual of suitable qualifications the opportunity of becoming a craftsman or a creative artist. In the social structure toward which we were now groping there could be no room for such as were forced to undertake tasks that were completely unattractive. If a man worked because otherwise he would want, then, being human, he would quite rightly work only for that time and in the least disagreeable way that in recompense would satisfy his needs. Without continuous and somewhat dangerous propaganda, the appeal to work in the service of and for the advantage of society could not be expected to appeal to very many people, and it certainly could not be expected to arouse the same feeling in individuals as did the invitation to work for the family or for the small social group. The objective should be the creation of a society in which the individual worked because he ardently wished to do so and because he found in his work complete satisfaction. It was wrong to give such emphasis as was now being given to the promise of reduction in working hours, of increased leisure, for this approach could mean nothing more or less than that work was to the great majority something which must necessarily remain distasteful. Nothing was more important than that this concept of work should be destroyed. Modernization meant far more than the re-equipment of a plant with new machines, far more than the introduction of new methods, it meant above all else a change of mind, and it was in this sphere that universities had their contributions to make to industry.

On June 18, Prof. C. F. W. Illingworth read a paper on peptic ulcer, based on a study of over 7,000 cases of perforated ulcer. The impression that perforation cured an ulcer had been proved false, as of 700 cases followed up no less than 70 per cent. developed a recurrence of the ulcer and 20 per cent. had severe complications. Of all forms of peptic ulcer, duodenal ulcer in males was by far the most common. In 60 per cent. of cases the onset was under 30 years of age, and symptoms had been present for an average of 7 years before the patient attended hospital. There had been

a considerable increase in the incidence of perforations during the war. The incidence dropped to about half from July to October in any year. Perforations were less common on Sundays and Mondays, and the most frequent hour for perforations to occur was 5 p.m. There was a widespread belief among many workers that their own occupation predisposed to the production of peptic ulcers. This disease had become common only during the past 40 years or so, probably as a result of increasing strain; the most hopeful line of future progress was in prevention.

Miss B. Grant, Canteen Supervisor at Anchor Mills, Paisley, followed with a talk on canteen services. In an address notable for its human approach, Miss Grant referred to the great increase in the number of canteen meals taken by employees during and after the war. There was difficulty in satisfying shift workers, and special arrangements should be made for juveniles, particularly the provision of extra food for those who were underweight. Meals should be served in attractive surroundings with a good colour scheme, but this would not camouflage a badly cooked meal. Miss Grant said that industrial workers were generally lazy eaters and food which required little mastication was preferred. She went on to describe workers' likes and dislikes for particular foods, with a survey of dietary requirements. There was no doubt that a good canteen service resulted in an improved standard of health in the factory.

NORTH-WESTERN GROUP

Chairman: Dr. E. Holland,
Mersey Docks Medical Service

Hon. Secretary: Dr. G. Taylor,
A. V. Roe and Co. Ltd.,
Greengate, Middleton, Manchester.

A meeting of the North-Western Group was held on April 10, 1948, through the courtesy of Messrs. Alfred Holt and Co., Blue Funnel and Glen Line, Liverpool, on board S.S. *Sarpedon*. Dr. E. Holland was in the Chair. Dr. F. A. Wilson, the Company's Medical Superintendent, addressed the meeting on industrial medicine in the shipping industry. He explained that the work of a medical superintendent was a different matter today as compared to some years ago, as he was concerned not only with the appointment of ship surgeons but with the examinations of all seafaring personnel and with the keeping of a complete record of the medical history of every man so that illnesses were followed up and he could ascertain that all were directed to the proper source to receive correct treatment; 9,000 examinations were carried out every year, apart from attention to sick and injured. Dr. Wilson said he was also concerned with general health matters concerning ships and was expected to give advice regarding accommodation, ventilation etc. There were also certain types of cargo carried, about which he had to see that ship surgeons were instructed with regard to medical hazards. He must also keep a careful watch on international health and deal with any epidemics which might break out aboard. Mention was also made of the compensation cases; these were examined primarily to report to the Company on their progress, but it was often possible to help by close contact with the general practitioner and hospital, and ready co-operation had been received from both these sources; special tribute was paid to the Dock Workers' Rehabilitation Centre at Manchester.

Dr. Wilson said that companies were no longer justified in paying ship surgeons very low wages, as these doctors had frequently to attend to serious cases on their own, and therefore great care was necessary in the selection of such men. A number of examples were given of the major operations which had been carried out by surgeons who had been compelled to rely on the assistance of one or more of the ship's officers.

The meeting concluded with a tour of S.S. *Sarpedon*.

SOUTH WALES AND WEST OF ENGLAND GROUP

Chairman: Dr. J. S. Snickett,
Messrs. Thomas and Baldwin Ltd.,
Ebbw Vale.

Hon. Secretary: Dr. G. Stenlake-Mundy,
The Bristol Aeroplane Co.,
Filton House, Bristol.

On May 14, after a short business meeting, the South Wales and West Group held their first Annual Dinner. The company of twenty-nine included Dr. Amor, President of the Association, and Prof. R. M. F. Picken, Professor of Preventive Medicine in the University of Wales.

Dr. Amor made a stimulating speech, and stressed the need for the University of Wales to undertake industrial research. Prof. Picken said that the Medical School would require more financial help before it could undertake work bearing on industrial problems.

There was a fruitful discussion on many problems associated with industrial health.

NOTTINGHAM GROUP

Chairman: Dr. G. E. C. Collis,
Messrs. Ransome, Marles Ltd., Newark.

Hon Secretary: Dr. J. Magill Young,
Brush Electrical Engineering Co. Ltd.

A dinner of the Group was held on Sept. 2, 1948, ten members being present. The Annual General Meeting followed, with Dr. G. E. C. Collis in the Chair. The Minutes of the previous meeting were read and approved. On the presentation of the Balance Sheet it was decided that the Group Representative to the Council should approach the Council on the question of expenses for attending Council Meetings, and whether these should be borne by the parent body or by the Group. In the event of the expenses being borne by the Group the annual subscription would have to be increased.

Dr. G. E. C. Collis proposed and Dr. I. R. Spark seconded that Dr. W. S. Whimster, Raleigh Cycle Co. Ltd., be elected Chairman for the year 1948–49. This was accepted unanimously.

Dr. J. Magill Young, Brush Electrical Engineering Co. Ltd., was re-elected Hon. Secretary and Group Representative to the Council.